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Walking Activity of Cardiac Patients during One-Year Post Cardiac Rehabilitation

Schrittaktivität von Herzpatienten im Laufe eines Jahres nach kardiologischer Rehabilitation

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Summary

› **Background:** Keeping patients active is an essential goal of cardiac rehabilitation (CR). This research aims to analyze the development of steps/day after CR.

› **Methods:** 126 adult, stable cardiac patients who had completed treatment for their acute condition, usually acute coronary syndrome or heart failure, were enrolled during CR and advised for daily step recording up to one year post CR. Mean number of steps during and for 3 weeks post CR were compared by paired t-test. Furthermore, influence of gender, age, smoking, NYHA, EF, BMI, day of the year, and length of time post CR on steps/day were estimated using a generalized additive regression model.

› **Results:** Compared to CR, steps/day increased on average by 925 steps/day in the first 3 weeks ($p<0.001$). Time post CR did not significantly affect walking activity (+0.35 steps/day, $p>0.05$), whereas seasonal correlations existed, indicating a summer increase and a winter decline ($p<0.001$). Mean steps/day during one-year post CR were reduced in female (-402 steps/day, $p<0.001$), older (-51 steps/year, $p<0.001$), overweight/obese patients (non-linear, $p<0.001$), in smokers (-725 steps/day, $p<0.001$) and ex-smokers (-1,119 steps/day, $p<0.001$), in patients with higher NYHA class (NYHA2:-1,216 steps/day, NYHA3:-1,946 steps/day, $p<0.001$) and EF group (EF2-4:-711 steps/day, $p<0.001$).

› **Conclusion:** Walking activity remains high during one-year post CR. Therefore, CR appears to exert a sizeable effect but needs to be pursued and individualized for further optimization.

KEY WORDS:
Pedometer, Physical Activity, Step Recommendation, Coronary Heart Disease, Heart Failure

Zusammenfassung

› **Hintergrund:** Körperliche Aktivität ist ein wichtiges Ziel kardiologischer Rehabilitation (REHA). Ziel dieser Studie war es, die körperliche Aktivität nach kardiologischer Rehabilitation, gemessen in Schritten/Tag, zu analysieren.

› **Methode:** 126 erwachsene, stabile Herzpatienten, die sich nach Akutbehandlung in REHA befanden, haben an der Studie teilgenommen und ihre täglichen Schrittzahlen bis zu einem Jahr nach REHA dokumentiert. In einem gepaarten t-Test wurde die durchschnittliche Schrittzahl/Tag während und in den ersten drei Wochen nach REHA verglichen. Zudem wurde der Einfluss von Geschlecht, Alter, Rauchen, NYHA, EF, BMI, Saison (Tag des Jahres) und Anzahl der vergangenen Tage nach REHA auf die tägliche Schrittaktivität mit einem Generalisierten Additiven Regressionsmodell geschätzt.

› **Ergebnisse:** Im Vergleich zur REHA-Zeit war die durchschnittliche Schrittzahl in den ersten drei Wochen danach um 925 Schritte/Tag erhöht ($p<0,001$). Die vergangene Zeitspanne nach REHA hatte keinen signifikanten Einfluss auf die Schrittaktivität (+0,35 Schritte/Tag, $p>0,05$). Diese variierte aber saisonal – Anstieg zum Sommer, Rückgang zum Winter ($p<0,001$). Die durchschnittliche Schrittaktivität/Tag im Verlauf eines Jahres nach REHA war bei Frauen (-402 Schritte/Tag, $p<0,001$), Älteren (-51 Schritte/Jahr, $p<0,001$), Übergewichtigen/Adipösen, (nicht-linear, $p<0,001$), Rauchern (-725 Schritte/Tag, $p<0,001$), Ex-Rauchern (-1.119 Schritte/Tag, $p<0,001$) und Patienten mit höherer NYHA-Klasse (NYHA2:-1.216 Schritte/Tag, NYHA3:-1.946 Schritte/Tag, $p<0,001$) und EF-Gruppe (EF2-4:-711 Schritte/Tag, $p<0,001$) herabgesetzt.

› **Fazit:** Die Schrittaktivität bleibt im Laufe eines Jahres nach REHA hoch. Demzufolge scheint REHA längerfristig zu wirken, sollte aber zwecks Optimierung fortlaufend aufgegriffen und individualisiert weiterverfolgt werden.

SCHLÜSSELWÖRTER:
Pedometer, körperliche Aktivität, Schrittempfehlung, koronare Herzerkrankung, Herzschwäche

Introduction

The participation of patients hospitalized after an acute coronary event or revascularization and of patients with heart failure in cardiac rehabilitation (CR) is a Class Ia recommendation from the European Society of Cardiology (26). A recently published study, which includes five years of follow-up, confirms its benefits in an unselected, real-world population by demonstrating that CR is associated with reduced hospitalizations for cardiovascular causes and cardiovascular mortality in patients after acute coronary syndrome or in coronary revascularized patients (11). According to another study, it seems to be irrelevant whether CR was conducted in an inpatient or outpatient setting. In terms of its ›

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Table 1

Demographic data of recruited patients: variable means (in brackets: empirical standard deviations).

	N	MEAN STEPS/ DAY DURING CR	MEAN STEPS/ DAY DURING THREE WEEKS POST CR	MEAN STEPS/ DAY DURING ONE YEAR POST CR	FITNESS (MAXIMUM WORKING CAPACITY [W/KG BODYWEIGHT] DURING CR)	AGE	BMI	DAYS OF PARTICIPATION POST CR
Total	126	6,633 (2,468)	7,558 (3,140)	7,562 (4,637)	1.54 (0.46)	60.45 (10.59)	27.18 (3.95)	262.83 (119.58)
Female	24	6,435 (2,339)	7,602 (3,253)	7,387 (4,292)	1.26 (0.39)	58.08 (9.73)	26.65 (4.73)	207.08 (123.45)
Male	102	6,679 (2,507)	7,373 (2,658)	7,592 (4,695)	1.61 (0.44)	61.01 (10.76)	27.27 (3.8)	275.95 (115.39)
NYHA1	95	6,931 (2,601)	7,979 (3,269)	7,886 (4,875)	1.65 (0.43)	60.06 (9.75)	26.9 (3.65)	272.59 (112.9)
NYHA2	24	5,809 (1,817)	6,444 (2,474)	6,532 (3,442)	1.29 (0.39)	63.17 (12.8)	26.82 (3.59)	249.67 (132.81)
NYHA3	7	5,410 (1,548)	5,671 (1,604)	5,788 (3,271)	1.02 (0.34)	56.43 (13.06)	34.44 (4.29)	175.57 (139.75)
EF1	101	6,668 (2,410)	7,703 (3,188)	7,728 (4,698)	1.53 (0.43)	59.88 (10.23)	27.47 (4.21)	262.22 (119.4)
EF2-4	25	6,490 (2,741)	6,976 (2,927)	6,900 (4,323)	1.58 (0.55)	62.76 (11.88)	26.15 (2.65)	265.32 (122.74)
Smoker	16	5,980 (2,093)	7,706 (3,781)	7,179 (5,058)	1.37 (0.38)	54.38 (8.4)	29.22 (6.53)	228.12 (130.31)
Ex-smoker	70	6,073 (1,958)	6,893 (2,699)	7,152 (4,325)	1.52 (0.44)	61.13 (10.53)	26.9 (3.53)	258.87 (121.3)
Non-smoker	40	7,874 (2,957)	8,665 (3,340)	8,340 (4,870)	1.66 (0.49)	61.7 (10.91)	26.91 (3.11)	283.65 (110.92)

benefits, no remarkable differences could be identified during one year post CR (31). Unfortunately, CR is underutilized (17), and adherence to activity recommendations in cardiac patients is poor after hospital discharge (18). The use of a pedometer could be a successful measure in helping cardiac patients stay physically active after CR (6). In an earlier study, steps per day correlated with physical and cardiological parameters in cardiac patients during CR, and steps per day were significantly reduced in patients who were unfit, older, smokers or ex-smokers (24). The aim of the current study was to analyze the development of steps per day over one year after CR and its relation to demographics (gender, age), time-related aspects (day of the year, length of time post CR), behavioral factors (smoking) and cardiovascular-disease-related parameters (NYHA class, ejection fraction (EF) , Body Mass Index (BMI)).

Methods

Stable cardiac patients attending three weeks of ambulant CR at the ambulatory facility, CCB-Herzwerk, in Frankfurt, Germany, between July 2015 and July 2016 were asked for study participation on admission. A total of 280 patients provided informed consent, approved by the Institutional Review Board of the Ethics Committee of the Hessian Medical Association. The CR program was multifaceted with a strong focus on exercise training (supervised endurance, resistance and gymnastic training, and sports games) and outdoor activities, such as hiking and Nordic walking. Exercise training consisted of daily ergometry – mainly cycling – (up to 30 minutes per day), strength training (1 hour per day), gymnastics (three to four units of 1 hour per week) and coordination training (1 hour, twice a week). Furthermore, classes promoting healthy lifestyle changes (healthy eating, smoking cessation, and staying active) and psychosocial consultancy were provided. Compulsory attendance was 6 hours per day, including 2 hours of recovery.

Exclusion

To ensure the capability of proper walking, 45 patients were excluded due to the following factors:

- peripheral arterial disease (n=18);
- neurological, orthopedic, and other relevant handicaps (n=23); and
- a combination of the above-mentioned criteria (n=4).

Measurements during CR

Smoking behavior, age, and gender: The smoking status – classified as a 'smoker', 'ex-smoker', or 'non-smoker' (never smoked) – age, and gender of the patients were recorded.

Exercise stress test: Before starting CR, each patient underwent a symptom-limited exercise stress test with electrocardiogram on a bicycle ergometer, asserting maximum Watt (W/kg bodyweight) with ergometers and monitors from Ergoline Ergoselect 400® (monitoring software: Ergoline ERS 2®).

NYHA classification: The admitting physician determined the patient's NYHA classification based on reported limitations during physical activity (12).

EF: The EF, calculated by Teichholz´s formula, was assessed during admission by echocardiography with General Electric Vivid Pro 7®, and the patients were categorized into four previously determined groups:

EF 1: > 55%
EF 2: < 55-45%
EF 3: < 45-35%
EF 4: < 35%

Pedometry during CR: Physical activity was assessed using pedometry. Therefore, pedometers (Omron Walking Style Pro 2.0®) were programmed with the patient's height and weight and blinded with black tape. Because permanent pedometry, except during swimming, showering, and sleeping, was desired, patients could wear the pedometer in their pockets, attached with a clip on a belt or a necklace. Despite the opportunity to wear it in different positions, the pedometer step counts are quite accurate (25). Small implausible daily step data (<100 steps/day) were rejected to avoid failure misreading. Additionally, patients were only included if they provided step data for more than 50% of their stay. After discharge, the patients were informed about their average steps per day during their entire CR, and – aside from the general exercise training

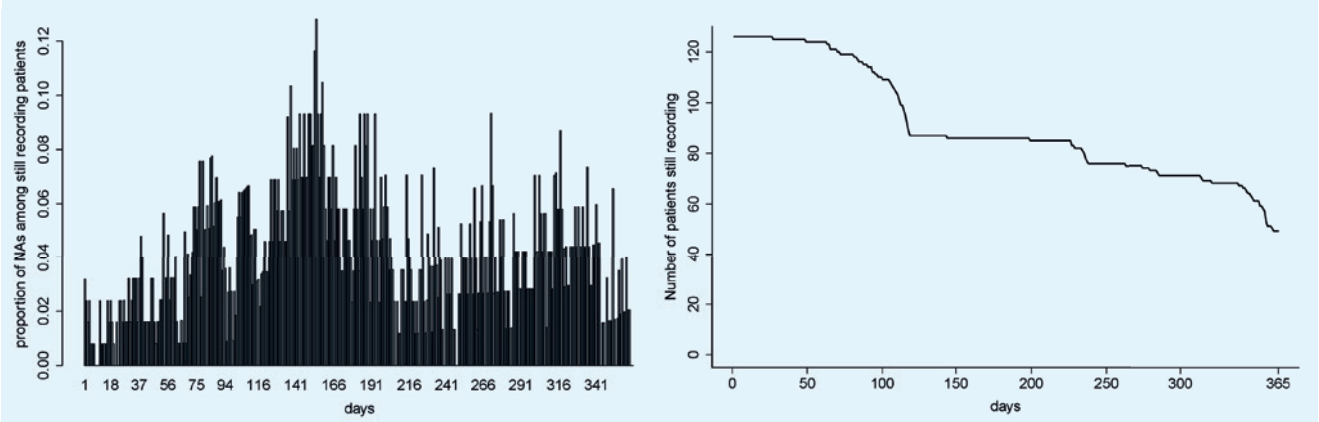

Figure 1

Proportion of missing records per day among patients still recording steps (left) and number of patients still recording over time (right).

recommendations from the medical staff – a step recommendation of >6,500 steps/day after CR was proposed to achieve the generally recommended amount of physical activity energy expenditure in secondary cardiovascular disease prevention (2).

Measurements after CR

Pedometry after CR: After discharge, the patients were asked to continue daily step recording in a heart diary for up to one year. Therefore, the pedometers were unsealed, and the patients were instructed about their usage. As in the assessment during CR, step data were only included if the patients provided step data for more than 50% during the time of participation. During this period, missing days were filled up with their per day step means. If patients stopped step recording, and therefore participation, step data were only considered up to that date.

Day of the year: In order to be able to understand if seasonal influences affect walking activity, date of CR-discharge was recorded, allowing us to evaluate steps/day on every single day of the year (1st of January=1, January 2nd=2, …).

BMI: Patients were encouraged to weigh themselves once a week. Hence, the Body Mass Index (BMI) could potentially vary over the time post CR. As for BMI missing values occurred, linear interpolation was applied where possible.

Statistical Analysis

T-Test: A paired t-test was performed to compare the walking activity of patients during CR with the initial activity afterwards. As 3 weeks of CR are usually provided in Germany, mean steps/day values of patients during CR vs. mean steps/day values during the first 3 weeks after CR were compared.

Kaplan-Meier: Kaplan-Meier-type curves were generated to visualize the relation between patients` mean steps/day and the length of time post CR (in days) in dependence on gender, NYHA class, EF, BMI-classification and smoking behavior. A further curve was created to illustrate seasonal relations by comparing the mean steps/day with the day of the year.

Regression analysis: A regression model was used to determine the relation between the parameters gender, age, smoking, NYHA, EF, BMI, day of the year, and length of time post CR with steps/day after CR. A genera-lized mixed additive model (GAMM) was used to account for individual-specific heteroscedasticity and potential non-linear effects.

R was conducted in statistical analysis (28), and the model was fitted using the gam(.) function from the mgcv package (36). The metric variables BMI and day of the year were included as smooth functions to account for potential non-linearity.

Results

Dropouts and Missing Data

Twenty-one patients aborted CR or cancelled the study. Furthermore, steps/day during CR of 22 patients could not be utilized because of missing data (technical problems or discontinuous pedometer wearing time). Another 66 patients quit after discharge (unwillingness to continue step recording after CR). As a result, the data from 126 patients could be analyzed. Figure 1 shows the number of patients continuing step recording over time and the proportion of their missing records per day. Their demographic data are described in Table 1. Due to the small sample size, the EF groups 2, 3 and 4 were combined in one group (EF2-4).

Statistical Findings

Steps/day averages during CR were 6,633 steps/day (SD 2,468) in comparison to a mean of 7,558 steps/day (SD 3,140) during the first three weeks after discharge. This initial increase of on average 925 steps/day (SD 2,150) had been highly significant ($p<0.001$).

Moreover, Kaplan-Meier-type curves were created in order to investigate the shape of walking activity in certain subgroups during one year post CR. A generally increased walking activity could be monitored in male patients (Figure 2), whereas activity was reduced in patients with higher NYHA class and EF group, in overweight and obese patients and in patients with a smoking history (curves not shown). Furthermore, length of time post CR did not really affect walking activity. On the contrary, the day of the year seems to influence the mean steps/day values, indicating an increase towards summer and a decline towards winter (curve not shown).

The observed tendencies in the Kaplan-Meier-type curves are consistent with the results of the regression model predicting the steps/day after CR. All effects were highly significant, except length of time post CR (number of days post CR) which was not significant and showed a negligibly low effect. A particularly high effect could be monitored in NYHA2 and NYHA3 patients. Their numbers of steps were strongly reduced compared to NYHA1 patients. The same holds for patients with a smoking history compared to non-smokers (never smoked), whereas walking activity was higher in smokers than in ex-smokers. Exact coefficient estimates are presented in Table 2. Nonlinear effects were found for BMI (Figure 3) and day of the year (Figure 4). The random intercepts of patients had an estimated variance of 2.085. ›

Table 2

Estimated coefficients of the linear regression effects on steps/day after CR obtained by an additive model with a nonlinear effect for BMI and day of the year.

PARAMETRIC COEFFICIENTS				
	ESTIMATE	STD. ERROR	t	PR(>|t|)
(Intercept)	11,300.4064	202.2174	55.882	<0.001
Sex	402.2686	92.8240	4.334	<0.001
Smoker	-724.9093	106.9525	-6.778	<0.001
Ex-Smoker	-1,118.5952	60.4657	-18.500	<0.001
EF2-4	-711.1455	71.8935	-9.892	<0.001
Number of day post CR	0.3508	0.2648	1.325	0.185
NYHA2	-1,216.3258	74.1067	-16.413	<0.001
NYHA3	-1,945.8471	169.8372	-11.457	<0.001
Age	-50.6129	2.7383	-18.484	<0.001
APPROXIMATE SIGNIFICANCE OF SMOOTH TERMS				
	EDF	REF.DF	F	P-VALUE
s(BMI)	8.4491	8.910	64.09	<0.001
s(day of the year)	7.6259	8.525	16.64	<0.001
s(ID)	0.9748	1.000	31.13	<0.001

Discussion

Mainly, this study confirms a reduced walking activity in females, in older patients, in patients with a higher NYHA classification and EF group, in overweight and obese patients and in patients with a smoking history during one-year post CR. Compared to the average walking activity during CR, an initial (3 weeks post CR) increase could be monitored post CR, whereas length of time after CR did not significantly affect walking activity of patients. On the contrary, the season seems to influence walking activity post CR, indicating an increase towards summer and a decline towards winter. In the following, the extent of walking activity after CR in general, its relationship with the parameters gender, age, smoking behavior, NYHA and EF and differences compared to activity during CR is discussed in detail.

Relation of Steps/Day with Gender and Age

In relation to activity during CR, males and females were able to maintain their number of steps per day post CR. Compared to each other, male patients ambulated a mean of 402 steps/day more than women after CR. The de- and re-increase in female patients (Figure 2, above 160; days post CR) could be explained by the reduced sample size at the end of the year and therefore, had to be judged as an irrelevant artefact. In general, there is evidence that males are physically more active than females (20, 33, 34). Furthermore, comparing the mean values during CR, fitness was higher in men than in women (24). However, lower fitness levels do not automatically lead to reduced activities. Therefore, practitioners should not simply accept their reduced activity and attribute it to physiological aspects. Many other factors like a different, maybe "gender-specific understanding of sport", social or educational aspects can be responsible.

Furthermore, both genders showed an activity decline with increasing age. Certainly, this tendency is in a way a natural development. However, regular physical activity contributes to maintain health, counteracts deterioration of chronic diseases and helps to preserve mobility and agility in the elderly (21). Furthermore, in this case the decrease refers to walking, which can be interpreted as a loss of mobility every single year. Therefore, older adults should be encouraged to attend activity on a regular basis, and it is mandatory to offer them specific and safe – if necessary, risk stratified – training programs. The same holds for women who could benefit from individualized "gender-adapted" measures, enabling them to get access to physical activities they like (self-realization). In general, regrettably, fitness of patients post CR could not be measured, and therefore, no reliable conclusions can be drawn regarding the effect on fitness by the number of steps/day after CR.

Relation of Steps/Day with Smoking Behavior, NYHA Class and EF Group

Concerning smoking, a reduced walking activity could be observed in ex-smokers and smokers compared to non-smokers. In general, smoking cessation is one of the most effective preventive measures regarding risk reduction in cardiac (e. g. coronary heart disease) patients (8, 10). However, only few studies analyzed if smoking status and physical activity could be directly related. A Tehran study, conducted in a healthy collective, showed that smokers exercise less and tend to physical inactivity (13). A further study describes a direct and negative effect of physical activity on smoking progression in adolescents and therefore suggests that physical activity could be a protective measure (1). Astonishingly, the negative effect for smokers was not as severe as for ex-smokers (-725 steps/day vs. -1,119 steps/day). An explanation could be that ex-smokers might have been more impaired and therefore, limited – assumable, their need for smoking cessation was higher. At this point it needs to be mentioned that the informative value of smoking behavior after CR is limited, because smoking status was only recorded during CR and possibly could have changed afterwards.

Besides demographic and behavioral relations, a lower walking activity after CR could be detected in patients with higher NYHA classification and EF group. This finding confirms observed tendencies during CR, although no significance was given during CR (24). A recently published study showed a significant difference of 1,629 steps/day in heart failure patients comparing NYHA2 and NYHA3 patients (3). Regarding the

mean steps/day values of NYHA2 and NYHA3 patients of this study, difference was less with only 744 steps/day and therefore, similar to the estimate of the regression analysis (730 steps/day), in which the influence of further parameters was taken into account. An explanation for this difference could be that the awareness for being active was more present in patients in poor general condition. They probably knew, because of their CR intervention, that they will significantly benefit even by a small activity increase (30). Furthermore, wearing time (2 weeks) and the chosen pedometer-type (wrist-worn) differed from this study (3). Anyway, the results of this study also confirm a decrease of walking activity from NYHA2 to NYHA3.

Walking Activity after CR

Many studies have shown seasonal and weather-related influences on activity (4, 7, 15, 16, 27). Therefore, the observed decline of mean steps/day values towards winter and its increase towards summer is not astonishing, but still important and interesting to notice, considering the fact that heart attack rates are higher in winter (22). Even though the reasons for this increase are unclear and other factors like the number of respiratory tract infections in winter or a triggering effect of the low temperature itself have been discussed, an activity decrease in winter cannot be beneficial. Therefore, medical practitioners should be aware of this decrease, point patient's attention to it and offer them training alternatives – like maybe indoor training.

Surprisingly, steps/day were initially increased after CR. One explanation could be that training during CR was not only step-based but also focused on resistance and exercise training, mainly conducted via cycle ergometer (up to 30 minutes per day). Another explanation for the higher walking activity after admission could be that pedometry was conducted unsealed, which has been linked with greater reactivity of patients in short-term pedometer studies (9). Apparently, CR itself has an effect on the number of steps afterwards. A mean of 7,562 steps/day during one year after CR could be rated as a positive CR outcome, presumably lowering risk profile (14). Patients seemed to be highly motivated to keep moving. Whether the increase leads to a physical activity energy expenditure change as well, and in which direction, remains unknown due to the limitations of activity assessment via pedometry, which is incapable of assessing non-walking and non-running activities and training intensities (23).

Although the decrement of positive CR-effects is a well-known issue (19), walking activity did not decline during one year after CR. On the other side, compared to long-term cardiac telerehabilitation programs – where pedometry and regular consultation were paired – no further significant increase of walking activity during one year after CR could be detected. Especially in a study where patients attended "regular" CR before and continued telerehabilitation afterwards, mean steps/day values increased from 8,673 to 10,236 during one year (35), whereas in a trial where patients did not attend CR before, an increase from 5,899 steps/day in the first week to 7,890 steps/day after one year was observed (32). Certainly, patients' collective in both trials differed and it cannot be excluded that other factors might have been responsible for the reduced walking activity of non-CR attendees. Nevertheless, there is enough evidence to believe that CR itself affects walking activity of patients afterwards in a positive manner, which is also supported by our results, showing an initial high activity after CR. Interestingly – besides patients' preference – it does not seem to matter if CR was conducted in an inpatient or outpatient setting. According to a study similar benefits regarding mortality, morbidity, event-free survival and a physical activity increase could be determined in both settings, settings 12 months afterwards (31). Contrary to our study, physical activity of patients was self-reported – via a self-questionnaire. For that reason, physical activity could be determined before CR, showing a significant increase afterwards. In our case, no comparison with physical activity before CR was possible. However, compared to CR, no decline could be observed over the year. ›

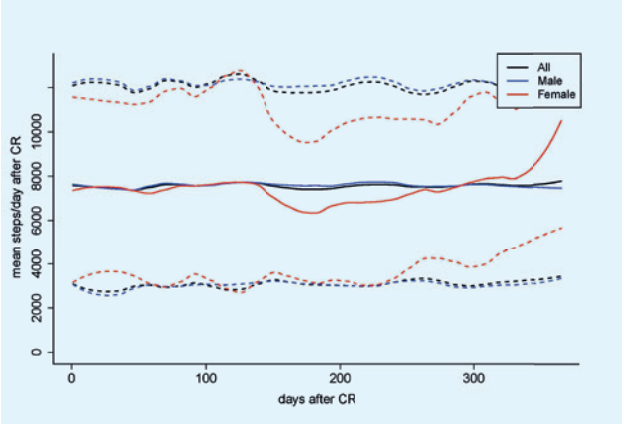

Figure 2

Mean steps/day (smoothed; solid line) ±one (smoothed; dashed lines) standard error after CR in male and female patients.

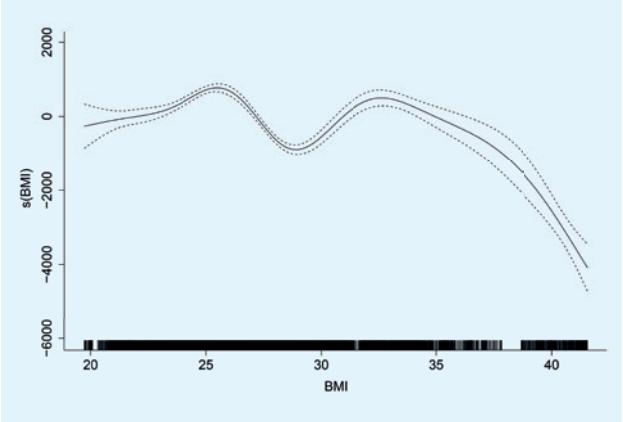

Figure 3

Steps/day mean values ±95% confidence interval after CR in dependence of BMI.

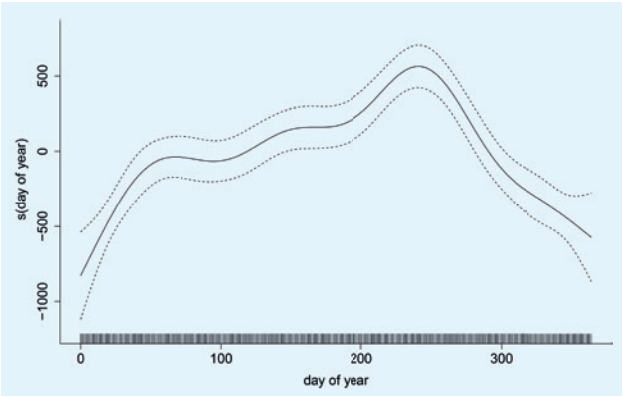

Figure 4

Steps/day mean values ±95% confidence interval during the course of the year (1st of January to 31st of December).

In summary, the results support the reasonability of pedometry in general (6) although – as a single measure – its usage does not suffice to raise physical activity in the long term. Consequently, this study underlines the importance of filling gaps in CR referral (5) and the necessity to implement further strategies after "regular CR" to enlarge effects.

Limitations

These study findings have some potential limits. First of all, our results describe the outcome after participation in an ambulant CR at CCB-Herzwerk in Frankfurt. CR in other centers, for example if conducted in an inpatient setting, could differ. However, there is some evidence that benefits are similar (31). Unfortunately, no data on patients' activity before CR are available. Therefore, a comparison of activities before and after CR was not possible. Furthermore, the steps per day after CR were correlated with some parameters recorded during CR (smoking behavior, NYHA classification, EF), which possibly could have changed afterwards. Due to the fact that patients were urged to wear the pedometer daily and record their step data up to one year post CR, dropouts occurred and lowered the number of participants. Therefore, the results must be treated with some caution. Furthermore, patients wore pedometers during non-walking/-running activities as well, which possibly could have led to miscounts because pedometry is only a suitable measure for counting steps (23). Actually, patients were asked to provide information about activities that do not accumulate in steps – like swimming, cycling or strength training. Regrettably, these recordings were afflicted with numerous missing values and, therefore, could not be analyzed in this study.

Conclusion

The most relevant finding is the initial increase of walking activity after CR and the detection that activity remains high during one-year. Therefore, CR is reasonable and, in general, efforts should be strengthened to reach patients with CR programs, which are underutilized despite proven evidence (29). In order to even raise physical activity afterwards, further measures like a CR refresher or at least telemetric ongoing consultations should be considered. Furthermore, the findings of this study imply a need for individualized CR strategies, focusing on getting and easing access to physical activities like indoor training possibilities in winter or gender-specific training, explaining impaired patients its benefits and offering smokers psychological consultation to quit smoking.

In future research it would be interesting to compare different types of sportive activities before and after CR in order to assess whether CR has led to the initiation of further activities.

Clinical Message

Walking activity did not decline during one-year post CR. Therefore, CR appears to exert a sizeable effect but needs to be pursued and individualized for further optimization.

Acknowledgement

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Conflict of Interest

The authors have no conflict of interest.

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