



Regular Article

# The effects of arm cranking exercise and training on platelet aggregation in male spinal cord individuals

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## ABSTRACT

Platelet aggregation at rest and in responses to exercise and training were compared between spinal cord injured (SCI) individuals ( $N=5$ ) and able-bodied subjects ( $N=7$ ). All participants performed arm cranking exercise at 60–65%  $VO_{2peak}$  for 30 min. Venous blood samples were obtained before and after sub-maximal exercise and measured for platelet aggregation using ADP and collagen. To assess the effects of arm cranking training, platelet aggregation was re-measured in all subjects at rest and in response to the sub-maximal arm cranking exercise after 12 weeks of individually supervised training programme. Before training, the resting mean values of platelet aggregation induced by ADP and collagen were not different ( $P>0.05$ ) between SCI and able-bodied. However the SCI individuals, but not the able-bodied subjects, exhibited a significantly ( $P<0.05$ ) higher maximal platelet aggregation induced by ADP and collagen following sub-maximal arm cranking exercise. Although  $VO_{2peak}$  after training was significantly increased ( $P<0.05$ ) in both groups, the resting mean values of platelet aggregation induced with ADP and collagen were not significantly different ( $P>0.05$ ) from those observed before training and were not different ( $P>0.05$ ) between SCI and able-bodied. Post-training, the SCI individuals, but not able-bodied individuals, exhibited a significant decrease ( $P<0.05$ ) in platelet aggregation following sub-maximal arm cranking exercise and this occurred with both ADP and collagen. These results suggest that SCI individuals, but not normal subjects increase their platelet aggregation following sub-maximal arm cranking exercise. Furthermore, arm cranking training in SCI individuals, appears to diminish the percentage of platelet aggregation ex vivo.

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## Introduction

Individuals with lower limb paralysis due to spinal cord injury (SCI) naturally use their arms for wheelchair locomotion and other activities of daily living, as well as for exercise training and sports activities [1]. The relatively small muscle mass under voluntary control, impaired cardiovascular reflex responses, and the inactivity of the skeletal muscle pump of the legs all lead to a diminished arm muscles ability to exercise. Furthermore, the weakness of the skeletal muscle results in premature onset of fatigue. This dampens an active lifestyle and daily life activities become more physically demanding to perform due to low level of muscular strength and cardiovascular fitness. Sedentary lifestyles worsen this condition leading a debilitating series of physical and cardiovascular complications that can be difficult to stop. Indeed, spinal cord injured (SCI) individuals suffer from a host of cardiovascular complications including coronary heart disease [2].

In recent years the involvement of platelets dysfunction in atherogenesis and the clinical complications from arteriosclerosis has become more recognised. Systemic platelet-related thrombogenic factors have been implicated in the initiation and subsequent development of atherogenesis and plaque formation [3,4]. Platelet aggregation is a complex process that is affected by a multitude of internal and external factors. Over the last two decades, interest has been heightened regarding the effects of exercise and training on platelet aggregation and function, not only in normal healthy subjects, but also in patients with different ailments particularly those with cardiovascular complications [5]. Although regular exercise has been shown to protect against coronary heart disease, the mechanism(s) through which it exerts this effect is not fully understood. Therefore the recognition of the effects of exercise on platelets is decidedly pertinent with respect to primary and secondary prevention of cardiovascular complications. Earlier reports on the effects of exercise on platelets aggregation and functions in normal healthy subjects have produced conflicting results [6]. However for patients with cardiovascular complications, particularly coronary heart disease, the balance of evidence available would suggest that platelet aggregation and activation are increased with exercise [2–5]. The exact effects of vigorous arm exercise and conditioning in SCI on platelet aggregation is not known.

Therefore studying the influence of exercise on platelet aggregation in spinal cord injured individuals may have clinical as well as scientific signifi-

cance because these individuals usually adopt physically inactive lifestyle and cardiovascular diseases are the most frequent cause of death in this population [7]. Therefore the present study was designed to examine the effects of arm-cranking exercise and conditioning of high intensity on platelet aggregation in spinal cord injured individuals in comparison with normal healthy subjects.

## Material and methods

### Subjects

Seven normal healthy subjects and five spinal cord injured individuals volunteered to participate in the study. All normal subjects and SCI individuals were untrained and followed a sedentary lifestyle. The subjects in the SCI group had a lesion level below T10. Of the five SCI, only one subject was a regular drug user who was also a cigarette smoker. The Ethics Committee of the institution approved the study protocol and testing procedures and all subjects signed an informed consent prior to the commencement of the investigation. All subjects took part in two sessions of habituation in order to familiarise themselves with the arm-cranking exercise protocol, testing procedures, and laboratory environment. Subjects age (mean  $\pm$  S.D.) was  $32 \pm 1.6$  years for normal subjects and  $31 \pm 2.9$  years for spinal cord injury individuals.

### Measurement of peak oxygen consumption ( $VO_{2peak}$ )

All subjects performed a continuous progressive workload arm cranking exercise test on arm cranking ergometer until volitional fatigue for the determination of  $VO_{2peak}$ . All subjects performed the  $VO_{2peak}$  test trial twice, 1 week before and 1 week after the completion of the conditioning programme. When subjects reported to the laboratory for testing, they were fasted for 12 h and had had no alcohol for the preceding 24 h. All tests and blood sampling commenced at the same time of day. Following a warm up period for 5 min at exercise intensity 30 W, the work rate was increased every 2 min by 30 W until exhaustion. During the test, a cranking frequency of 60–65 was maintained by using metronome. Minute ventilation, oxygen uptake, and carbon dioxide production were continuously sampled and analysed by an open-circuit system (Metamax, Cortex, Germany). Calibration of the system was carried out

according to the manufacturer instructions. Heart rate was measured at rest and continuously during exercise by short-range radio telemetry (Polar, P.E. 3000, Kempele, Finland). The physiological data obtained from the peak oxygen consumption ( $VO_{2peak}$ ) test were utilised, using regression analysis, for the calculation of the exercise intensity corresponding to 60–65%  $VO_{2peak}$  for each subject. The indication for termination of exercise was subjective maximal exercise as indicated by the participants' own symptom of fatigue or breathlessness. Other indication for stopping the exercise was the occurrence and progression of any symptoms to the point of unwillingness of the subject to proceed further or that continuation of the test might be detrimental to the subjects' welfare. The attainment of  $VO_{2peak}$  was judged when the following criteria were met (1) a plateau in  $VO_2$  with increasing the workload, (2) inability of the subject to maintain the designated pedalling frequency, (3) a respiratory exchange ratio of 1.1 or above. If a subject did not complete a satisfactory maximal test, the testing procedures were repeated after 7 days.

### **Sub-maximal arm cranking exercise test protocol before conditioning**

Approximately 1 week after the measurement of  $VO_{2peak}$  each subject performed a sub-maximal exercise protocol. The exercise protocol consisted of a warm-up period for 5 min at 30 W, thereafter the external work load was increased to elicit a physiological response corresponding to 60–65%  $VO_{2peak}$  and arm cranking exercise continued at this intensity for 30 min. A cranking frequency of 60–65 per minute was maintained and heart rate was monitored continuously by a telemetry heart rate monitor (Polar, P.E.3000, Kempele, Finland).

### **Exercise conditioning programme**

The conditioning programme was individually supervised for each subject in both the SCI and control groups. All exercise sessions were performed using arm-cranking ergometer and each training session started out with a 5-min warm-up at a light workload. Thereafter, the workload was increased to elicit a heart rate corresponding to 60–65  $VO_{2peak}$  for each subject. The external resistance to arm cranking during each training session was continuously adjusted to maintain the pre-assigned intensity and all subjects exercised at this intensity for 30 min. The exercise sessions

were continuous, and supervised and monitored regularly. Each subject's training heart rate was adjusted as sub-maximal heart rate was decreased training. All exercise trials and training sessions were performed in a temperature-controlled environment ( $22 \pm 2$  °C). All subjects exercised for 30-min on three non-consecutive days/week for 12 weeks. No dietary changes were recommended, but subjects were instructed to consume their normal diet and maintain their normal activity and lifestyle patterns throughout the study. The attendance rate was 100% in both the SCI and able-bodied groups. During the conditioning programme, all subjects were instructed to follow their normal routine and refrain from strenuous exercise.

### **Sub-maximal arm cranking exercise test protocol after conditioning**

The same sub-maximal arm cranking exercise, as described above, was used after conditioning to determine the effects of exercise and training on platelet aggregation at rest and in response to acute exercise. Although the subjects' cardiorespiratory fitness was improved due to conditioning, the acute arm cranking following conditioning was performed at the same relative exercise intensity in relation to  $VO_{2peak}$  (60–65%  $VO_{2peak}$ ).

### **Blood sampling and analysis**

Blood sampling occurred at the same time of day in an ambient temperature of  $20 \pm 2$  °C and relative humidity of  $55 \pm 5\%$ . All subjects were given well in advance explicit instructions to refrain from food, caffeine or strenuous physical activity during the 12 h preceding the blood sampling. After reporting to the laboratory, subjects were requested to remain in the sitting position for 15 min, after which a resting 10 ml of venous blood sample was obtained with no stasis. The resting blood sample was taken before any warm-up exercise and was kept in crushed ice until the completion of the sub-maximal exercise before and after conditioning. A second 10-ml blood sample was removed immediately after the sub-maximal arm cranking exercise test (60% of  $VO_{2peak}$ ). Blood was transferred in to tubes containing 3.8% trisodium citrate dihydrate (4.5 ml blood to 0.5 volume of citrate). Tubes were mixed gently and thoroughly and platelet rich plasma (PRP) and platelet poor plasma (PPP) were prepared by centrifugation. Citrated blood was centrifuged for 5 min at  $400 \times g$  to obtain PRP,

then the blood sample centrifuged again at  $2000 \times g$  for 20 min to acquire PPP. Autologous PPP was used to adjust the platelet count of PRP to  $200 \times 10^9/l$  before measurement of platelet aggregation was made. Approximately 30 min after blood sampling, platelet aggregation was measured with a four-channel aggregometer (PAP-4, BioData, UK). Aggregation of PRP was induced by ADP and collagen (with final concentrations of  $2 \times 10^{-5}M$  for ADP and collagen) at  $37^\circ C$  with continuous stirring by a magnetic stirrer. Both resting and post exercise blood samples from each subject were analysed together. Over the duration of the study, blood samples were coded and analysed using the same batch of ADP and collagen. The aggregating agents ADP and collagen were used as agonists because of differences in the mode of platelet response. Collagen being a potent agonist inducing platelet release from the three granuli populations, while ADP is a weaker platelet agonist that stimulates a release only from the dense and alpha granule but not from the lysosomes. The initial light transmission of PRP was set at 0%, while that of PPP was set at 100%. Maximum aggregation (percent of maximal light transmittance after the addition of the aggregating agent) was determined.

### Statistical analysis

All statistical analyses were performed using the software statistical package SPSS version 11 (SPSS, Chicago, USA). A two-way analysis of variance (ANOVA) with repeated measurements was used to detect differences in mean values. When ANOVA indicated the presence of overall significant difference, Tukey's post hoc tests were employed to ascertain which mean values were statistically significant. The alpha level of  $P < 0.05$  was the minimum level required to reject the null hypothesis.

Values in the text are mean  $\pm$  S.D. unless otherwise stated.

## Results

### Physiological results

Spinal cord individuals and normal subjects were of similar age with no differences in resting lipid profiles (unpublished data). Table 1 presents physiological and performance-related data before and after the conditioning programme in SCI individuals and able-bodied subjects. Before the conditioning programme,  $VO_{2peak}$  and maximal exercise duration and exercise intensity achieved were similar for the two groups. All SCI and able-bodied subjects exhibited a significant increase in  $VO_{2peak}$  and in maximum exercise duration and intensity following training. Thus indicating that the physical conditioning programme had induced favourable cardiovascular improvements with a resultant significant increase in the maximal aerobic capacity.

### Platelet aggregation at rest and following acute sub-maximal arm cranking exercise before conditioning

The resting and post sub-maximal arm cranking exercise mean results of platelet aggregation studies with ADP are shown in Fig. 1. The resting mean values of platelet aggregation induced by ADP were not different ( $P > 0.05$ ) between SCI individuals and normal healthy subjects. Compared to rest, the SCI group exhibited a significantly ( $P < 0.05$ ) higher maximal platelet aggregation induced by ADP following strenuous arm cranking exercise. In contrast, strenuous arm cranking exercise had no

**Table 1** Physiological responses to maximal arm cranking exercise before and after training in SCI individuals ( $N=5$ ) and able-bodied subjects ( $N=7$ )

	SCI individuals		Normal subjects	
	BT	AT	BT	AT
$VO_{2peak}$ ( $l \text{ min}^{-1}$ )	$1.81 \pm 0.10$	$1.94 \pm 0.05^*$	$1.82 \pm 0.11$	$2.1 \pm 0.1^*$
$VO_{2peak}$ ( $l \text{ kg}^{-1} \text{ min}^{-1}$ )	$24.12 \pm 2.60$	$26.2 \pm 1.36^*$	$26.79 \pm 1.85$	$29.1 \pm 1.05^*$
$HR_{peak}$ (beat/min)	$173 \pm 8.2$	$173.2 \pm 10.8^*$	$169 \pm 5.9$	$169.8 \pm 7.3^*$
$VE_{peak}$ ( $l \text{ min}^{-1}$ )	$75.3 \pm 9.1$	$83.56 \pm 10.2^*$	$68.4 \pm 5.4$	$80.3 \pm 7.7^*$
$WL_{peak}$ (W)	$168 \pm 37.6$	$185 \pm 24.1^*$	$160 \pm 16.5$	$204 \pm 11.2^*$

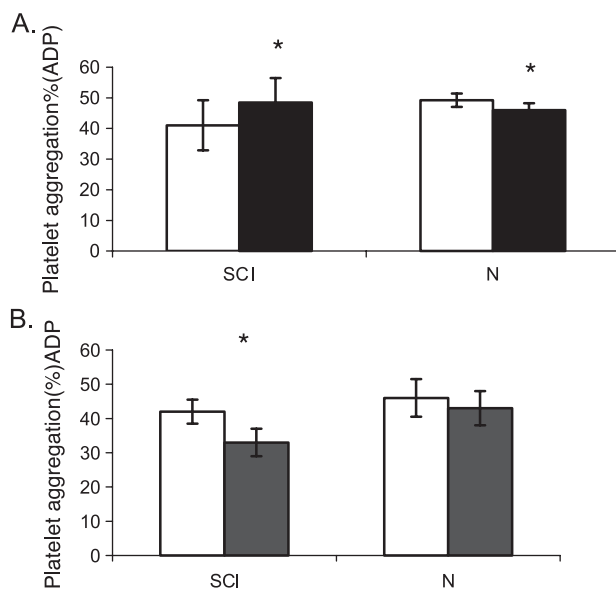
$VO_{2peak}$  = maximum amount of oxygen consumed at the end of the incremental arm cranking test.  $HR_{peak}$  = maximum heart rate achieved at the end of the incremental arm cranking test.  $VE_{peak}$  = maximum ventilation at the end of the incremental arm cranking test.  $WL_{peak}$  = maximum workload achieved at the end of the incremental arm cranking test. BT = before training and AT = after training. \*Significant difference ( $P < 0.05$ ) compared to before training.

significant effect ( $P>0.05$ ) on platelet aggregation induced by ADP in normal subjects.

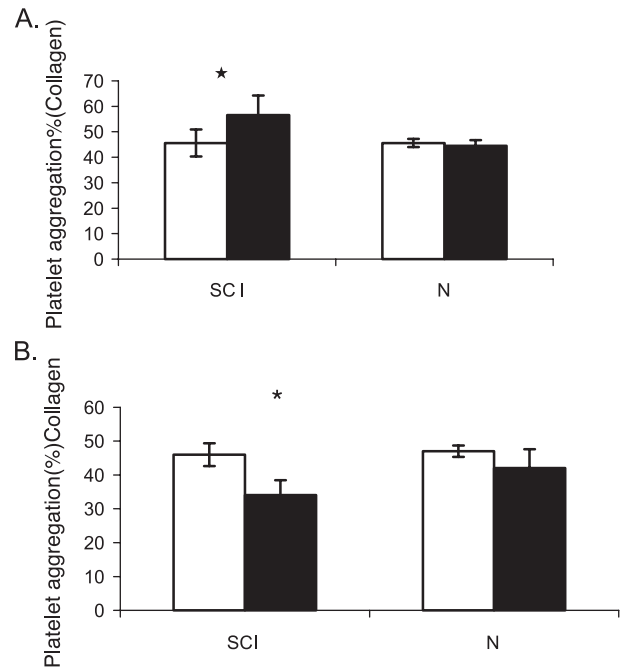
The resting and post sub-maximal arm cranking exercise results of platelet aggregation studies with collagen are illustrated in Fig. 2. Resting mean values of maximal platelet aggregation induced by collagen were not significantly different between SCI individuals and normal subjects. Following strenuous arm cranking exercise; maximal platelet aggregation induced by collagen increased significantly in SCI individuals. In contrast, maximal platelet aggregation with collagen in response to exercise was not altered by exercise in normal subjects.

### Platelet aggregation at rest and following acute sub-maximal arm cranking exercise after conditioning

The resting mean values of platelet aggregation induced by ADP before training were not different ( $P>0.05$ ) from those observed after training and were similar between SCI individuals and normal healthy subjects. In contrast to the results obtained before training, individuals in the SCI group exhibited a significantly ( $P<0.05$ ) lower maximal platelet aggregation induced by ADP following strenuous arm cranking exercise. In normal subjects, the mean value of maximum platelet aggregation following strenuous arm cranking ex-



**Fig. 1** Mean ( $\pm$  SE) values of platelet aggregation (%) with collagen at rest (open bars) and after arm cranking exercise (solid bars). SCI = spinal cord injured; N = normal subjects. A represent before training and B represent after training. \*Statistically significant difference.



**Fig. 2** Mean ( $\pm$  SE) values of platelet aggregation (%) with ADP at rest (open bars) and after arm cranking exercise (solid bars). SCI = spinal cord injured; N = normal subjects. A represent before training and B represent after training. \*Statistically significant difference.

ercise after training was not significantly different ( $P>0.05$ ) from that found before exercise and was not affected by training (Fig. 1A and B).

Similar to ADP, the resting mean values of platelet aggregation induced by collagen before training were not different ( $P>0.05$ ) from those observed after training and were similar between SCI individuals and normal healthy subjects. In contrast to the results obtained before training, individuals in the SCI group exhibited a significantly ( $P<0.05$ ) lower maximal platelet aggregation induced by collagen following strenuous arm cranking exercise. In normal subjects, the mean value of maximum platelet aggregation following strenuous arm cranking exercise after training was not significantly different ( $P>0.05$ ) from that found before exercise and was not affected by training (Fig. 2A and B).

## Discussion

Numerous studies have been conducted on the effects of exercise and training on blood haemostasis [1–5], but few studies were carried out to ascertain such effects in SCI individuals; particularly those related to platelet aggregation and activation [8]. The results of the present study

suggests that (a) platelet aggregation at rest appears to be similar between SCI and able bodied individuals and is not affected by training, (b) strenuous bout of arm cranking exercise is associated with a significant increase in platelet aggregation in SCI individuals, but not in able bodied subjects and (c) arm cranking training in SCI individuals appears to significantly suppress platelet aggregability following acute bout of arm cranking exercise. These results clearly demonstrate that arm cranking exercise training is associated with favourable effects on acute exercise-induced changes in platelets aggregation in SCI individuals.

Platelet aggregation is a complex process that is affected by a multitude of internal and external factors [3–5,9]. The majority of previous clinical and pathological studies have indicated that platelets play a fundamental role in the pathogenesis of thrombosis and atherosclerosis [9]. Data showed that platelet aggregation induced by ADP and collagen at rest in SCI subjects did not differ significantly from those of able-bodied individuals. However acute bout of arm cranking exercise was followed by a significant increase in platelet aggregation only in the SCI individuals. The enhanced platelet aggregation in response to an acute bout of arm cranking exercise in the SCI group may accelerate the thrombogenic process in the coronary microcirculation. It may also contribute to the pathogenesis of thrombosis; particularly as increased platelet aggregation may also enhance blood coagulation [3]. It is therefore possible that, as a result of exercise intolerance in the SCI group, the sub-maximal exercise intensity and duration employed in the study herein was sufficiently stressful to trigger direct increase in platelet aggregation.

Although physical exercise is widely recognised as being beneficial to health, attempts to relate the effects of exercise to changes in platelet aggregation have produced conflicting results [3,5,9–11]. The present work describes arm-cranking exercise and training related responses of platelet aggregation in SCI individuals and normal subjects, but it does not offer additional information on the possible mechanism(s) responsible for these responses. Although the exact mechanism(s) responsible for this phenomenon is not clear, it might be related to catecholamines particularly epinephrine. Earlier reports indicated that strenuous exercise is associated with epinephrine release [11] in those individuals with SCI below T10, as it is the case in the present study exhibit a higher sympathoadrenal activity than the normal non-injured individuals. Therefore it is reasonable to suggest that enhanced platelet aggregation by an

acute bout of intense arm cranking exercise might have been caused by endogenous release of epinephrine in SCI group but not in the control. In vivo experiments indicated that SCI individuals exhibit greater P-selectin than normal subjects. It could also be argued that the arm cranking exercise bout employed in the present study was associated with higher level of P-selectin and consequently higher platelet aggregation and activation. Although P-selectin was not measured in the present study, previous studies indicated that P-selectin is increased in response to arm cranking exercise in SCI individuals but not in able-bodied subjects [8]. It is generally accepted that platelets activity and aggregation is highly variable even within the normal population, and it is important to take into account that platelet activation in the SCI individuals may be secondary to areas of ischemia developing in leg microcirculation. Additionally, influences of metabolic or hormonal adaptations are also significant variables in the regulation and behaviour of platelet aggregation and activation in SCI individuals.

It is probable that acute arm cranking exercise in SCI individuals, but not in normal subjects, resulted in the mobilisation of recently produced and metabolically more active platelets from the pulmonary vessels. These platelets exhibit raised activity of monoamine oxidase and elevated aggregation potential [3,5]. Lactic acidosis has also been implicated in exercise-associated increase in platelet aggregation as high correlation between the increase in hydrogen ion concentration and platelet aggregates was reported [3]. The exact role of lactic acidosis in exercise-induced alterations in platelet aggregation cannot be deduced from the data of the present study and further investigations are needed. Additional hypotheses have been suggested to elucidate the mechanisms through which exercise induced alteration in platelet aggregation. For example, Sakita et al. [12] suggested that the enhanced platelet aggregation might be linked with a decrease of platelet sensitivity to endothelial-derived nitric oxide, probably due to a reduction in its availability. However, this clarification appears implausible in light of the evidence reported by Tozzi-Ciancarelli et al. [13], who demonstrated an increase in nitric oxide availability after strenuous exercise with concurrent increase in platelet aggregability. Thus, it appears that SCI individuals, but not normal subjects, increase their platelet aggregation following sub-maximal arm cranking exercise.

In contrast to reports on the acute effects of exercise, only few data are available on the influence of regular exercise training on platelet aggrega-

gation and function. The training programme of the present study was associated with a marked improvement in the cardiorespiratory system as reflected by a significant increase in the peak amount of oxygen consumed at the end of maximal exercise. There was also proof of improvement in performance as indicated by an evident increase in the maximal exercise duration and the workload accomplished at the end of the maximal test (Table 1). These improvements in cardiorespiratory fitness and performance related indices occurred in parallel with a significant reduction in platelet aggregation in response to arm cranking exercise in SCI individual. In the past only few experimental trials were conducted to determine the effects of physical training on platelets in able-bodied men and women [14,15]. The data generated from these studies suggested that exercise training of moderate intensity in young able-bodied males and females is associated with diminished platelet adhesiveness and aggregation at rest and in response to an acute bout of vigorous exercise. Interestingly, men exhibited augmented platelet aggregation before training in response to acute exercise, but this response was attenuated following training [14]. The beneficial effects of training on platelet aggregation at rest and in response to exercise were no longer apparent with detraining both in men [14] and in women [15].

In partial agreement with the above studies, arm cranking exercise training in SCI individuals, appears to suppress platelet aggregability following acute bout of arm cranking exercise (Figs. 1 and 2). The acute platelet aggregability response to arm cranking exercise and the beneficial effects of training were consistent and occurred in all SCI individuals. An earlier study in overweight, mildly hypertensive middle-age men also showed that physical training of moderate intensity was associated with desensitisation of platelets [16]. Likewise, the known unfavourable adverse effects of ageing on platelets appear to be attenuated with physical training [17]. Although the precise mechanism(s) by which physical training desensitise platelet is not completely understood, this could be attributed to an increase in prostacyclin and/or nitric oxide; both of which are known to be potent inhibitors of platelet aggregation. This may have been associated with, and contributed to, physical training induced desensitisation of platelet in response to exercise [14,15,18].

In conclusion, the results of the present study demonstrate that SCI individuals, but not normal subjects increase their platelet aggregation following sub-maximal arm cranking exercise. Furthermore, arm cranking training in SCI individuals,

appears to suppress platelet aggregability following acute bout of arm cranking exercise.

It is recognised that the small number of SCI individuals participated in the study limits the results obtained. This was mainly due to difficulties of recruiting SCI individuals who were capable of performing arm cranking exercise for the duration of the study. It is important to repeat this type of study with a larger number of subjects, and at different environmental conditions (hot and cold), with additional measurements including catecholamines and objective markers of in vivo platelet activation such as beta thromboglobulin and platelet factor 4. The failure to construct a dose–response curve for platelet agonists may be a limitation as there is absence of specific intervention designed to elucidate potential mechanism(s) involved. Further studies should also focus on the potential mechanism of the interaction between platelet aggregation and exercise and training in this population. The results of these studies would further our understanding of the effects of exercise and training on platelet aggregation and function in SCI individuals. It is equally important, given the complexity of the haemostatic system, that future studies should examine arm cranking exercise and training effects on blood coagulation and fibrinolysis in parallel with platelet aggregation and function.

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