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Can FES-rowing mediate bone mineral density after spinal cord injury: A pilot study

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Abstract

Following spinal cord injury (SCI), bone mineral density (BMD) is lost at a rate of ~4% per month reaching a peak at ~6 months post injury. A new intermediate plateau is reached at ~16 months post injury at ~50% of pre injury levels. This is reported to be at, or near known fracture thresholds. This explains the high incidence of non-traumatic fractures in this population which predominate in the distal femur and proximal tibia. Numerous pharmaceutical and non-pharmaceutical studies have sort to address this life-threatening secondary condition of SCI. Here we report a novel form of physical therapy using Functional Electrical Stimulation (FES)-assisted rowing. The training volume (3x 30 min FES-rows and 4x 60 min leg conditioning sessions per week) and intensity (~80% of $\dot{V}O_{2res}$) used in this pilot study appears to mediate BMD in the knee in a chronically trained FES-rower. Longitudinal repeat measure studies with greater numbers are now required to confirm the effect this form of training is having, and identify if the training volume and intensity used in this study is optimum for this population. (179 words)

Introduction

Osteoporosis is a known secondary complication of SCI characterised by low bone mineral density (BMD) which is primarily lost below the level of lesion in the load bearing lower limbs (Biering-Sorensen, Bohr, & Schaadt, 1988, 1990; Dauty, Perrouin Verbe, Maugars, Dubois, & Mathe, 2000; Garland et al., 1992; Maimoun et al., 2005; Roberts et al., 1998; Szollar, Martin, Parthemore, Sartoris, & Deftos, 1997; Zehnder, Luthi, et al., 2004). Loss of BMD is the result of deterioration in bone micro-architecture (Modlesky, Majumdar, Narasimhan, & Dudley, 2004), geometric structure and strength (Modlesky, Slade, Bickel, Meyer, & Dudley,

2005; Rittweger, Goosey-Tolfrey, Cointry, & Ferretti, 2010), and altered mineralization and collagen matrix composition (Chantraine, Nusqens, & Lapiere, 1986). These factors explain the high incidence of pathological fractures in the lower limbs (Eser, Frotzler, Zehnder, & Denoth, 2005) which predominate in the distal femur and proximal tibia (Fattal et al., 2011; Freehafer, 1995; Zehnder, Luthi, et al., 2004).

Loss of BMD in the lower limbs starts from the first day of injury and decreases at ~4% per month (Wilmet, Ismail, Heilporn, Welraeds, & Bergmann, 1995) peaking at ~6 m post injury (Maimoun et al., 2002; Wilmet et al., 1995). A new plateau is reached at ~16 months post injury with BMD approximately half that of pre-injury values (Dauty et al., 2000; Garland et al., 1992). This is reported to be near fracture threshold according to the work of Eser and co-workers (Eser et al., 2005). In this study, ninety nine motor complete participants were questioned about the occurrence, location and approximate date of any fractures to the lower limbs. Trabecular and cortical BMD, as well as bone geometric properties of the distal epiphyses and mid-shafts of the femur and tibia were measured by peripheral quantitative computed tomography (pQCT). Fractures had occurred in twenty one out of the ninety nine participants; these individuals had trabecular BMD of less than 114 mg/cm^3 and less than 72 mg/cm^3 in the femur and tibia respectively. These data imply that there is a fracture threshold of ~110 mg/cm^3 in the distal femur and ~70 mg/cm^3 in the proximal tibia, above which no fractures have occurred and below which fractures due to minor trauma are common (Eser et al., 2005).

The underlying mechanisms behind osteoporosis in SCI are complex and are still the subject of research (Jiang, Jiang, & Dai, 2006). For example, bone loss occurs in the normally loaded and innervated upper limbs in patients with paraplegia and tetraplegia which suggests that hormonal change mechanisms are involved (Finsen, Indredavik, & Fougner, 1992; Frey-Rindova, de Bruin, Stussi, Dambacher, & Dietz, 2000). In addition, recent work suggests that bone re-modelling is regulated by nerve-derived signals as well as

neuromediators such as noradrenalin (Elefteriou, 2005). However, nerve-derived mechanical-unloading is generally considered the primary pathogenesis of osteoporosis in SCI (Frost, 2003a, 2003b).

De-mineralized bones in SCI can fracture spontaneous or with low energy during everyday activities such as wheelchair transfers (Eser et al., 2005). Fractures in persons with SCI are not only costly in terms of hospitalisation (Lippuner, Golder, & Greiner, 2005), fracture risk complications (Morse et al., 2008) and surgery, which can be problematic due to the low BMD and casting that can cause pressure ulcers (Nottage, 1981; Ragnarsson & Sell, 1981), but can also severely reduce the quality and quantity of life of the individual (Fattal et al., 2011). The hazard for mortality is estimated to be 78% higher for people with SCI who sustain a lower extremity fracture than their peers without fractures (Krause, Carter, Pickelsimer, & Wilson, 2008). In view of this, recent research has focussed on improving bone mineral density by pharmacological and non-pharmacological approaches.

Whilst pharmaceutical interventions using bisphosphates such as alendronate have been shown to slow the resorption of bone immediately after injury by selectively inhibiting osteoclasts (Zehnder, Risi, et al., 2004) their efficacy remains low because of the limited number of studies investigating small numbers of patients. In addition, bisphosphates have no effect on increasing bone mass after it has been lost (Zehnder, Risi, et al., 2004). A number of important questions remain unanswered regarding pharmaceutical interventions such as the ideal timing of treatment, whether the treatment should be short or long-term, and whether intravenously administered bisphosphonates would be more appropriate. As a consequence, clinicians remain reluctant to prescribe pharmacological bone treatments (Ashe, Craven, Eng, & Krassioukov, 2007).

Other research has focused on physical therapy as a more natural method of mediating bone loss. However, it is unknown whether bone loss after SCI is due to insufficient

osteogenic loads or if it is the result of neurogenic changes (Shields et al 2006). In the SCI model, it is not possible to deliver loads that exceed an osteogenic threshold without the use of neuromuscular electrical stimulation (NMES). However, rehabilitation strategies to preserve bone loss after SCI involving lower-limb loading using NMES such as cycling (Bloomfield et al 1996; Eser et al 2003) and treadmill walking (de Bruin et al 1999) have shown little or no effects on BMD. It is possible that these methods may not have delivered sufficient threshold loading and or loading frequency. In the neurologically intact human model, biomechanical stresses determine the shape, size and composition of bone (Frost 1987; Wolff 1986) and bone density responds to the magnitude of strain in a dose-dependent manner (Lu 1997). Further, it is muscular contraction, not body weight that presents the largest bone and joint forces in the intact human model (Lu 1997).

Although the dose-response in the SCI model is unknown, Shields and co workers (Shields et al 2006) determined that compressive loads of ~1 to 2 times body weight, induced by muscle contractions, are required to partially prevent loss of BMD after SCI. In their study, 6 subjects with complete paralysis completed a 3-year unilateral plantar flexor muscle activation programme. Tibia compressive force in the trained limb was > 140 % of body weight. In a parallel study by this research group, two AIS A SCI subjects were found to have increased BMD in the neck of femur (male 23, C5, 2 years FES-rowing trained ~22 %; male 56, T4, 6 years FES-trained ~15 %) following routine annual health checks. These findings motivated the present study the aims of which were to: 1. Establish the magnitude of joint contact forces (JCF) imposed on the upper and lower limbs following chronic FES-rowing training. 2. Establish the dose-response required to mediate bone loss after SCI. 3. Determine if a risk of fracture exists when FES-rowing. We hypothesise that: 1. JCF in the upper and lower limbs will increase as a result of FES-rowing training. 2. The training protocol of 3x 30 min rows and 4x 60 min leg conditioning sessions per week is sufficient to attenuate BMD decline in the limbs exposed to the active muscle training. 3. That the FES-

rowing training protocol used in this study does not present a risk of fracture of the lower limbs.

Methods

The rowing machine used for the trials was a Concept 2 model D which has been adapted for people with spinal cord injury (SCI) by our group (Andrews, Hettinga, Gibbons, Goodey, & Wheeler, 2007; Hettinga, 2007; Wheeler, 2002). The rowing machine was fitted with a telescopic leg stabilizer to restrict movement of the legs to the sagittal plane and a high backed padded seat to which the subject was strapped to provide upper body stability. The track was inclined forward by 3.8 degrees to assist the return to catch. Electrodes (Pals + 3 inch round, Axelgaard Inc, USA) were placed to stimulate the components of rectus femoris, vastus lateralis and vastus medialis anterior to the thigh and components of semimembranosus, semitendinosus and biceps femoris posterior to the thigh. The electrodes were activated by a 4-channel muscle simulator (Type ST-04-CH, Odstock Medical Limited, Salisbury, UK) adapted for use with an external control switch. The stimulator provided a monophasic output pulse (50Hz, pulse width 250μs with adjustable current 0-115mA. The control switch was mounted onto the handle of the rowing machine and activated by the subject such that when pressed stimulation was applied to extend the leg for the drive phase and when removed to flex it for the recovery phase.

The force being applied to the handle of the rowing machine by the hands was measured using an in-line strain gauge based force transducer located (type, manufacturer, range **) in series with the tethering chain. The original foot rests on the rowing machine were removed and brackets were located in their place which was cantilevered from 2 floor mounted AMTI force plates (Fig 1). The force plate measures forces and moments in 3 orthogonal directions allowing the force vectors at each foot to be calculated together with its line of action.

Fig 1: Footplates cantilevered from floor mounted force plates.

The posture of the subject was measured using a Vicon 3-dimensional optical tracking system (Vicon Oxford UK, www.vicon.com). 37 retro-reflective markers were attached to the subject at prescribed locations on anatomical landmarks (Fig 2). The subject was surrounded by 12 cameras at known positions which enabled the calculation of the position of the markers in space via a direct linear transform [ref]. From the location of the markers, a biomechanical model of the subject was used determined in order to calculate the joint articulations. Markers were also attached to the rowing machine and the handle so the line of action of the force in the tethering chain could also be determined.

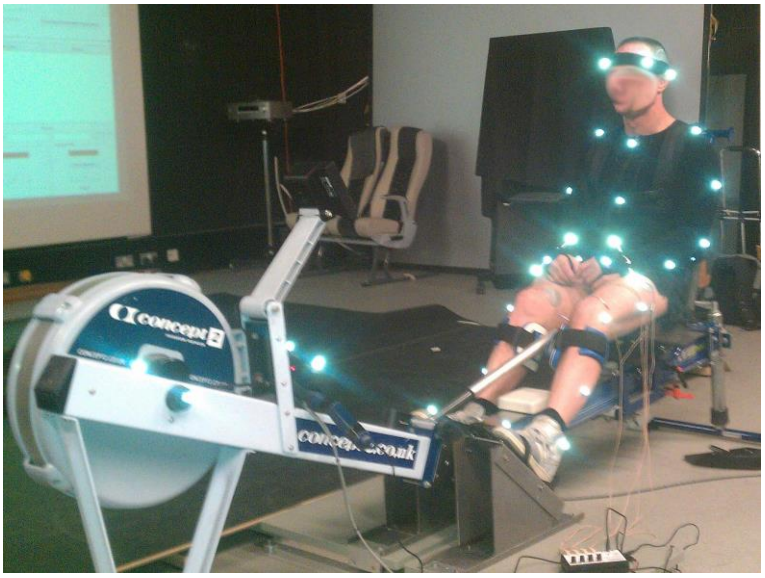

Fig 2: Subject with retro-reflective markers attached for motion capture.

The measured joint articulations were used to animate a subject in the Biomechanics of Body (BoB) muscle modelling package (Shippen & May, 2010). The BoB package calculates the muscle force distribution by calculating the torque at the joints based on the geometry and motion of the skeletal mechanism, the mass distribution of the subject and the external forces acting at the feet and hands. The forces acting at the seat were not considered as it is assumed that there are no external loads parallel to the track on which the seat moves and hence dissipates no power. Additionally, the scalar product of the force acting normal to the track with the velocity of the seat along the track is zero and hence dissipates no power. These assumptions were confirmed by noting that when the foot and handle forces resolved along the direction of the track where divided by the acceleration of the centre of mass the quotient was within 10% of the subject's body mass.

The musculoskeletal model consisted of 36 rigid segments connected by 34 joints which were selected to represent their physical counterpart. For example the elbow was modelled as a hinge, the hip joint as a spherical joint, and the knee as two rolling surfaces. Inverse dynamics approach was used to calculate torques at each of the degrees of freedom at the hip, knee and ankle. The fully defined muscle model consisted of 652 muscle units however

for this analysis only the muscles which were stimulated by the Odstock stimulator were included in the analysis; rectus femoris, vastus medialis, vastus lateralis anterior to the thigh and semitendinosus, semimembranosus and biceps femoris posterior to the thigh. As there are more muscles than torques in the analysis there is not a unique solution for the muscle force distribution. Therefore an optimisation approach is employed. The chosen optimisation function is to minimise the sum of the square of the muscle activation where muscle activation is defined as the quotient of the instantaneous force and the maximal isometric force of the muscle. This optimisation echoes the physiological strategy of minimising fatigue. The optimisation is also subject to the equality constraint that the individual muscle torques acting across a joint must sum to the torque at the joint. Additionally, the inequality constraints specify that the muscles cannot generate a force greater than their maximal isometric force and the force in the muscle must be greater than zero; that is they cannot push.

To represent the muscle loading of the subject, the BoB model was modified to permit only forces to be generated in the rectus femoris, vastus lateralis and vastus medialis anterior to the thigh during the drive phase of the rowing cycle, and semitendinosus, semimembranosus and biceps femoris during the recovery phase. The inverse dynamics analysis resulted in the forces of constraints at the joints. However the muscles which cross the joints and generate the torques at the joints also increase the joint contact forces. As the loads in the muscles were calculated in the previous analysis step, the joint contact forces from the inverse dynamic analysis were augmented by the vector summation of the loads in the muscles which cross the joints.

The subject and co-author (RG) for these trials was a 56 year old, 75 kg male, height 1.72 m with a T4 AIS (American Spinal Cord Injury Impairment Scale) grade A spinal cord injury and was 10 years post injury. RG had been chronically FES-trained for 8 years. The 20 week FES-training programme has been described previously (www.fesrowing.com). Following the

initial training, RG has FES-trained on average 6 times per week comprising of 2-3 FES-rowing sessions for 30 mins and 3-4 FES-leg conditioning sessions for 60 mins. Following a standardised warm-up period of 5 minutes, the subject rowed with a power indicated on the rowing machine monitor of 70W for a period of 30 seconds for each trial with recovery periods of 5 minutes between trials. Two rowing styles were adopted, differing in the timing of the handle control switch. Style A has minimal or no overlap between quadriceps stimulation and handle pull which facilitates the return to catch. Style B has a maximal overlap between quadriceps stimulation and handle pull.

Results

Peak compression and shear forces in the active knee joint (Figure 4 C & D) were found to be above the known osteogenic threshold (Shields, Dudley-Janoroski, & Frey Law, 2006) and greatest when using the overlap rowing style (Figure 4 D). Further, compression and shear forces in upper and lower limbs were greatest using the overlap technique.

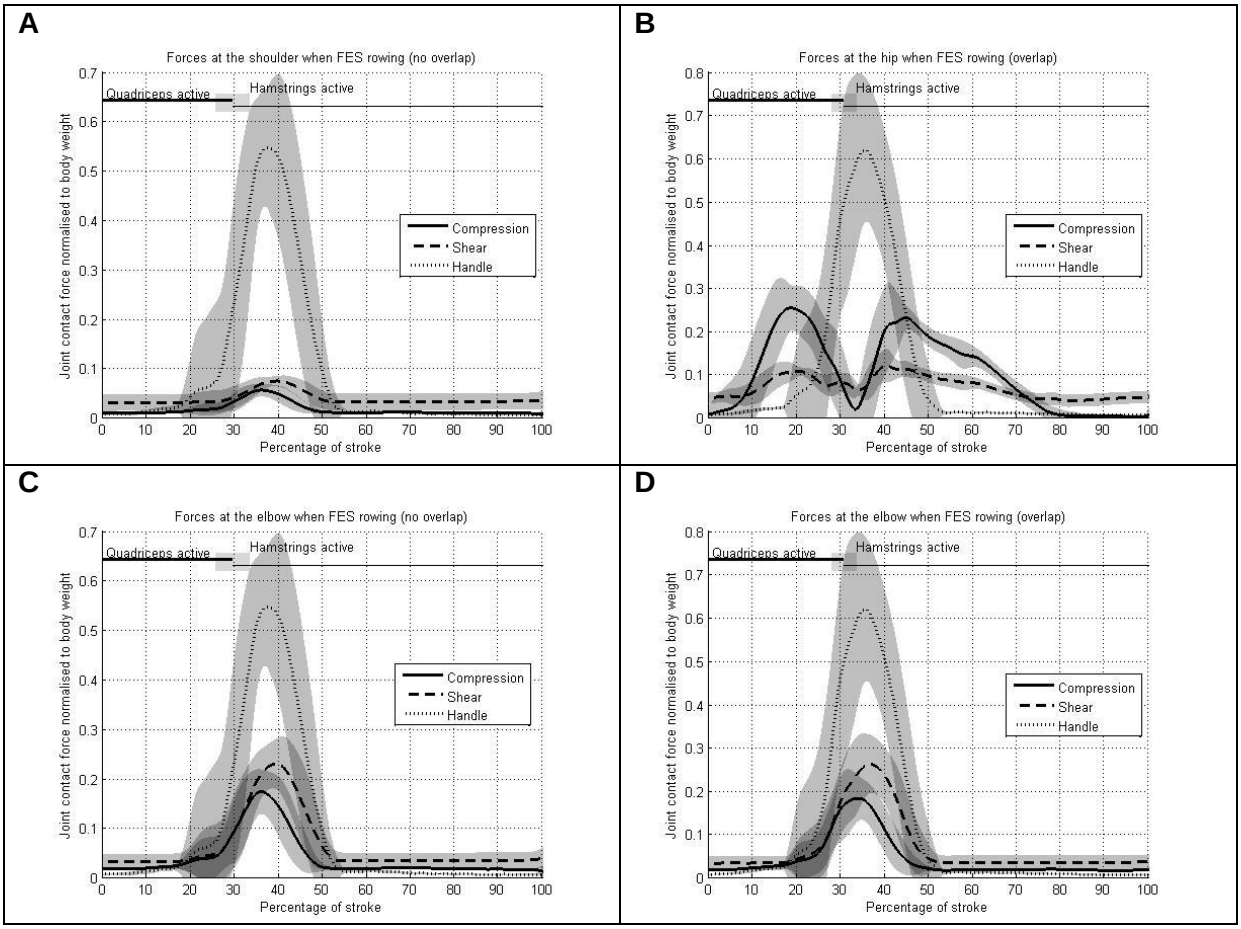

Figure 3: Compressive and shear forces normalised to body weight at the shoulder with no-overlap (A) and overlap rowing style (B) and elbow with no-overlap (C) and overlap rowing style (D) at 70 W indicated power output. Joint contact forces are normalised to body weight. Subject: 56 years old, 75 kg male, height 1.72 m with a T4 AIS grade A spinal cord injury, 10 years post injury.

In the upper limbs, a single peak handle force (~0.62 x BW vs. ~0.55 x BW) compression force (~0.19 x BW vs. ~0.18 x BW) and shear force (~0.22 x BW vs. ~0.26 x BW) in the active shoulder and elbow joints was higher using the overlap rowing technique (Figure 3 B & D). Handle and compression force development occurred at the same point in the stroke whilst the shear force development occurred ~4% later. The overlap peak forces in both joints also occurred earlier in the stroke (~34% to 37% vs. 36% to 40% of stroke) and were greatest at the elbow.

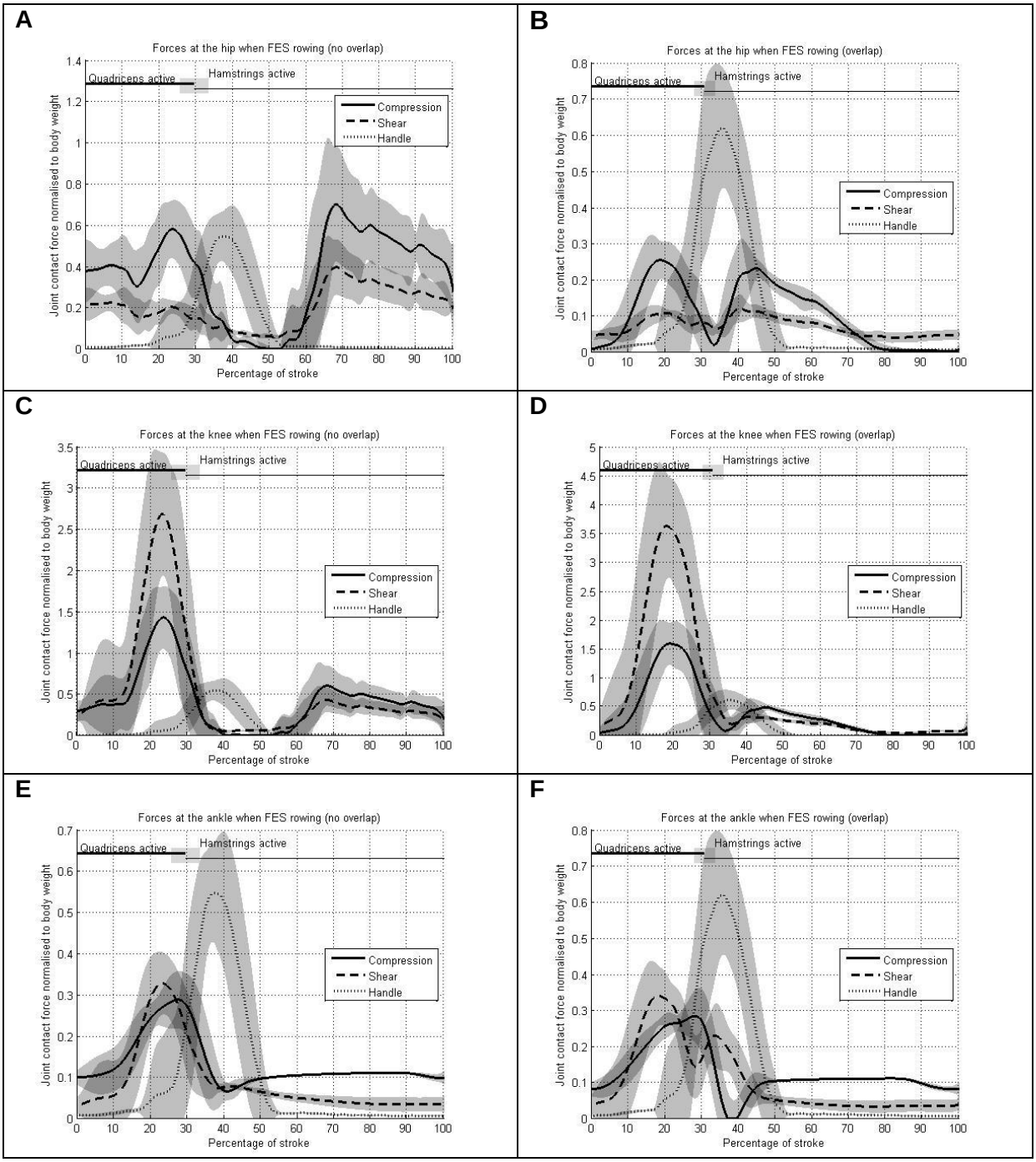

Fig 4: Compressive and shear forces normalised to body weight at the hip with no-overlap (A) and overlap rowing style (B), knee with no-overlap (C) and overlap rowing style (D), and ankle with no-overlap (E) and overlap rowing style (F) at 70 W indicated power output. Joint contact forces are normalised to body weight. Subject: 56 years old, 75 kg male, height 1.72 m with a T4 AIS grade A spinal cord injury, 10 years post injury.

In the lower limb joints, although the peak handle force in the overlap technique mirrored the same higher value earlier in the stroke as in the upper limb joints, the resultant joint contact

force (JCF) development in the inactive hip, active knee and inactive ankle joint was different regardless of rowing technique. Further, in all lower limb joints, compression and shear forces had two peaks, unlike the single peak force seen in the upper limbs. This was most pronounced in the inactive hip joint.

In the inactive hip joint, both initial peak compression (~0.59 x BW vs. ~0.26 x BW) and peak shear (~0.2 x BW vs. ~0.1 x BW) forces were greatest with the non-overlap rowing style. This is contra to the knee and ankle joints and requires further investigation. Further, the peak compression forces are greater than the peak shear forces which is again contra to the knee and ankle joints. This may be due to the type of joint; universal ball and socket in the inactive hip joint, and hinge joint in the active knee joint which may minimised shear. A second peak compression (~0.7 x BW vs. ~0.23 x BW) and peak shear (~0.0.4 x BW vs. ~0.12 x BW) force is seen during recovery. It is hypothesised that these secondary peak forces are due to hamstring contraction, but it is not known why they are greater during the non-overlap rowing style. This also requires further investigation.

In the active knee joint, the first peak compression (~1.6 x BW vs. ~1.4 x BW) and shear force (~3.6 x BW vs. ~2.7 x BW) was greatest with the overlap technique during the drive phase (Figure 4 C & D). A second lower peak compression (~0.5 x BW vs. ~0.6 x BW) and shear (~0.3 x BW vs. ~0.4 x BW) force was seen during the recovery phase. The second peak compression and shear force developed significantly earlier in the stroke (~45% vs. ~68%) during the overlap technique.

In the inactive ankle joint, the first peak compression and shear force were of a similar value during both rowing techniques (Figure 4 E& F). However, the first peak compression (~30% vs. ~28%) and shear (~18% vs. ~23%) force occurred earlier in the stroke when using the overlap rowing technique. A second peak compression (~0.1 x BW) force was seen in the

recovery phase during hamstring stimulation whilst the shear force continued to decrease in value.

Discussion

Considering the magnitude of the peak compressive and shear forces being developed with the present 4-channel system, there has not been a single reported case of lower limb fracture related to FES-rowing. This is likely explained by the mechanostat hypothesis (Frost, 2003b). In the first instance, the mechanostat includes two tissue-level mechanisms; bone modelling which increases whole-bone strength and remodelling which turns bone over in basic multi-cellular units (BMU's) (Frost, 2003a). Its "disuse-mode" reduces bone strength by removing tissue close to or next to the marrow (Frost, 2000). Loads on bones cause strains that generate signals that some cells can detect and to which they or other cells can respond (Skerry, 2002). Genetically determined threshold ranges of these signals help control modelling and remodelling. When bone strains exceed bone's modelling threshold range (MTR), modelling can switch on to strengthen a load bearing bone (LBB).

In addition, healthy load-bearing bones (LBB) have more strength than is needed which keeps typical peak voluntary mechanical loads (TPVML) from causing non-traumatic fractures. TPVML are defined as the "largest repeated and intentional loads on bones exerted by intentional activities during a normal week or month" (Frost, 2003b). As such, TPVML are mainly generated by intentional repeated skeletal muscle contractions.

Furthermore, load-bearing bones (LBB) have a natural strength-safely factor (SSF) (Alexander, 1984; Cowin & Weinbaum, 1998; Currey, 2003; Frost, 2003c) that defines how much more strength they have than the minimum needed to keep the typical peak voluntary mechanical loads (TPVML) from breaking them suddenly or in fatigue. Frost suggests that the SSF could define the LBB's "bone-strength to bone-load" ratio. In healthy free-living humans, LBB largest normally-allowed strain or stress caused by TPVML's is determined by

a bones modelling threshold range, or minimally effective strains (MES) (Frost, 2001). Providing MES are less than a bones fracture strength threshold (FST), a strength-safety factor must exist, or SSF = FST / MES. Expressing FST and MES as stresses, a healthy young human LBB should have ~6 times more strength than the minimum needed to keep TPVML's from breaking them (Frost, 2001).

In FES-rowing, initial training begins with severely atrophied lower limb musculature. The force generating capacity of these muscles is consequently very low. Most resent data from this group shows typical untrained knee extension muscle forces of 30 to 40 N in a 35 year old female with a C4 AIS A injury. As the muscular strength increases, the compressive and shear forces increase proportionally. For example, following ~8 months leg conditioning and FES-rowing training the knee extension forces in this subject had increased to 50 to 70 N representing ~40 % force increase. These increasing forces will progressively mechanically load the long bones of the lower limbs. In the case of the experienced FES-rower in this pilot study, the peak knee compression and shear loads are ~1.6 and ~3.6 time's body weight respectively. It is highly likely that the modelling threshold range mechanism still functions in SCI at what Frost terms the lower re-modelling threshold range (RMES) (Frost, 2003b). This lower range has been brought about by the complete loss of mechanical loading. However, as the TPVML have increased with electrical stimulation of the quadriceps and hamstring muscle groups, the RMES would respond by increasing the natural range of strain and stress to more normal levels.

Notwithstanding the increased fatigue issue with the overlap rowing Style (2), both techniques result in greater loading of the active knee joints as seen in Figure 4 C & D when compared to the loading of the inactive hip and ankle joints. In addition, regardless of rowing technique or active vs. inactive joints, the lower limbs are subject to two peak forces unlike the single upper limb peak forces. The first peak compression and shear forces seen in the hip, knee and ankle joints appears to be the result of quadriceps contraction extending the

knee joint during drive. The second peak compression and shear forces occur during late handle pull as the rower reverses direction from drive to recovery. We hypothesis that these forces are the result of the hamstring muscles flexing the knee joint during recovery which is part evidenced by the knee compression forces (~0.5 x BW) being greater than the shear forces (~0.3 x BW).

Fatigue in the legs is of concern since this will influence potential limb loading. There are a number of contributory factors. When the stimulation to the quadriceps is maximal (115 mA with the present 4-channel Odstock muscle stimulator), the legs are not able to contribute further to the muscle force being developed. Any change in indicated power at this point can only come from voluntary activation of upper-limb musculature. This is achieved by an increase in cadence, or a change in rowing style. The experienced rower in this study has developed two distinct rowing styles. Style (1) is the standard non-overlap technique taught novice rowers. This style uses an accelerated arm pull in late drive / early recovery, coincident with the change from quadriceps stimulation to hamstring stimulation. This technique assists the return to catch (Andrews et al, 2012). Style (2) is an overlap technique which uses a similar accelerated pull but earlier in late drive. This technique results in additional loading of the lower limbs and is especially marked in the active knee joint as shown in Figure 4 C (no-overlap) and 4 D (overlap) coincident with a reduction in stroke rate. Excessive loading of the lower limbs using this Style (2) results in overload-type muscle fatigue.

In addition, it is highly likely that the cardiorespiratory system is unable to deliver sufficient pressure and therefore oxygen delivery to sustain the metabolic demands of the lower limbs which would contribute to premature fatigue. With the current motor point-type stimulation, motor axons from peripheral pathways are recruited. As intensities increase, antidromic transmissions block any motor neuron recruitment from a more stable central sensory pathway (Bergquist et al 2011). At the point of hand switch release, the motor point

stimulation to the quadriceps muscles instantaneously stops resulting in the cessation of the peripheral (motor axon) pathway leaving only momentary central (sensory axon) pathway contribution once the inhibitory antidromic transmission has stopped. This requires further investigation.

Conclusion

Our data shows that FES-rowing results in active knee JCF loads that are believed to attenuate bone mineral density and bone mineral content (Shields et al 2006). Further, in a parallel study by this research group, two experienced FES-rowers were found to have increased BMD in the inactive hip joint following routine annual health checks. These findings support our hypotheses that 1. JCF in the upper and lower limbs will increase as a result of FES-rowing training and 2. The training protocol comprising of 3x 30 min rows and 4x 60 min leg conditioning sessions per week provides sufficient force magnitude and force loading to attenuate BMD decline in the limbs exposed to the active muscle training. 3. That the FES-training protocols used in this study appear to load the lower limbs with forces and force rates that are below the rate of osteogenesis and do not therefore present a risk of fracture of the lower limbs. Further work is now required to optimise lower limb force loading of the active joints, coincident with multi-channel systems which activate hip and ankle joints.

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