Ekso Robotic Exoskeleton Clinical Research Summary of Findings

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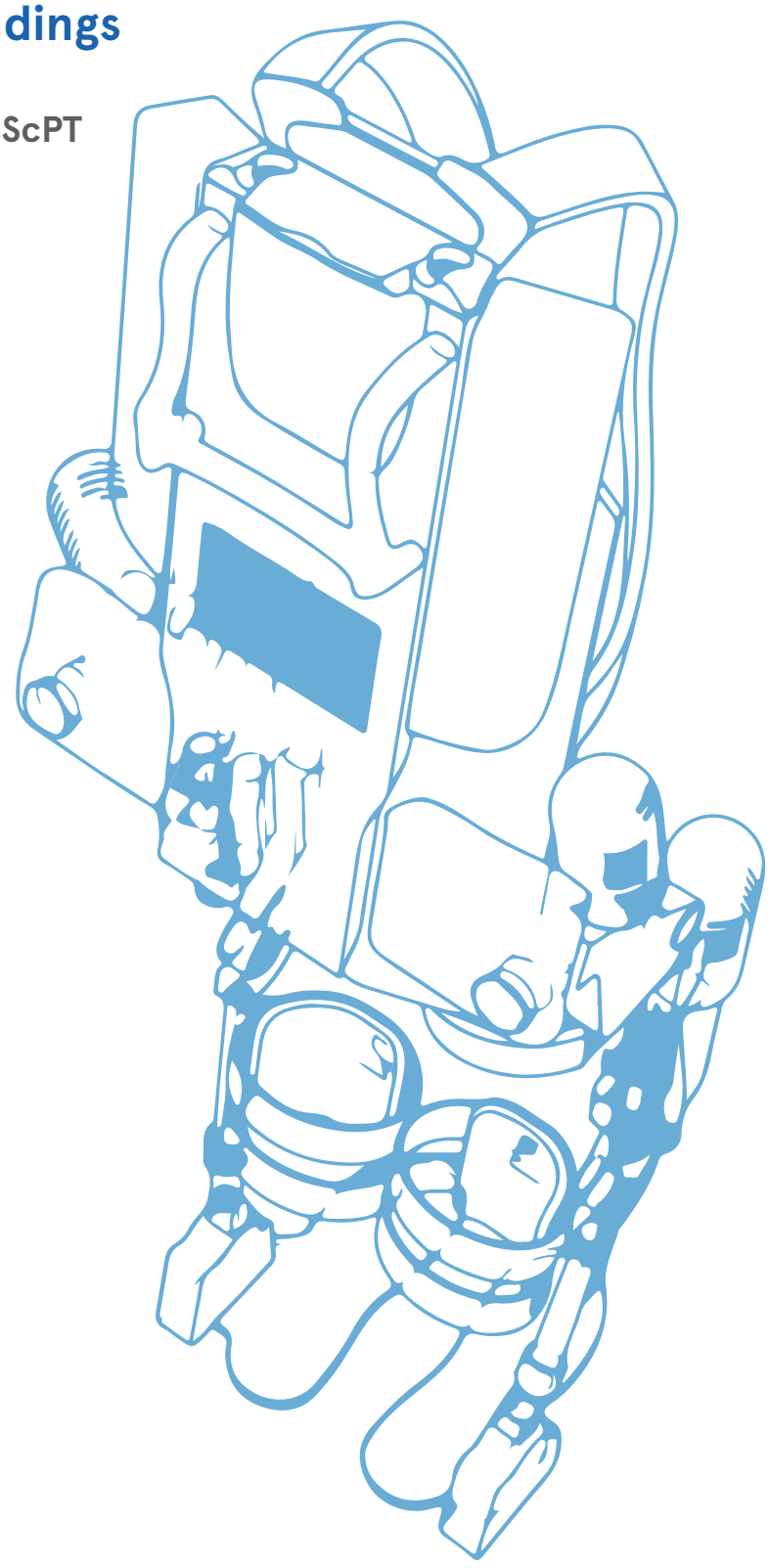

Ekso Robotic Exoskeleton Research Update – 2017

Updated Numbers

Research with Ekso (referring to both first (Ekso1.1) and second (EksoGT) generation robotic exoskeletons) has grown in 2017. Currently, 62 studies (up from 55) have been completed or are ongoing internationally: 35 are completed, 27 are ongoing; and 6 are multi-center. These studies include the following diagnoses: spinal cord injury (SCI) (37), stroke (13), multiple sclerosis (3), traumatic brain injury (2), cerebral palsy (1), and multiple diagnoses (6). Total target enrollment is over 1,250 participants, with over 550 completed to date. Nine SCI studies and one stroke study have been published with several more in these and other diagnoses expected in the remainder of 2017. Ekso has been included in five published review articles[1-5] and one book chapter.[6]

Ekso and Walking

Ekso continues to demonstrate safety, progression of walking, and feasibility in a variety of diagnoses and settings (n=219).[7-13] An additional study has supported users' learning curve of 15 sessions for walking with contact guard assist or close supervision (n=11).[9,14] Preliminary data from an ongoing trial with Ekso in SCI[10] and a systematic review[15] supported previous findings[16] that actual and perceived cardiorespiratory effort could be minimal or taxing during robot assist gait training walking, depending on level of volitional activity and walking speed. Thus, users can reap the benefits of walking with reduced cardiovascular fatigue and risk or with increased cardiovascular challenge.

Recently presented data further supported increased gait speed (n=31)[9,10,14,17-20] and timed walking distance (n=23),[9,10,17-19,21] as well as improved balance (n=18)[19,22,23] while walking in Ekso, mostly for those with *complete* SCI. Of note, McIntosh[10] showed 3 of 4 participants walked in the device faster than the threshold for limited community walking (0.44 m/s) for SCI. Ramanujam et al.[20,23] determined that increased step and stride lengths and decreased stance time were highly correlated to increased gait speed in exoskeletons (n=11). Notably, Ekso was able to activate trunk and leg musculature below the level of injury in those with complete SCI (n=8)[23,24], adding to their postural control of weight shifts in Ekso. In those with *incomplete* SCI, Ekso targets muscle activation of proximal and posterior lower extremity muscles (n=14).[23,25] Gait speed in this group measured outside of the device pre-post training has also been shown to significantly increase (n=29).[26-28] Preliminary data[27] has shown gait speed improvement in participants with sub-acute to early chronic incomplete SCI (n=20), nearly meeting the minimal clinically important difference (MCID) for slow walkers (0.15 m/s)[29] and the threshold for limited community walking (0.44 m/s).[30] Significant improvements in timed walking distance (n=37)[27,28,31] and walking balance (n=4)[28] have also been shown for this diagnosis.

Ekso has been shown to increase gait speed (n=30)[32-33] and walking distance (n=23).[32] in *stroke*. Molteni et al.[32] described effects in people with sub-acute (n=12) and chronic (n=11) stroke after training 3x/wk for 4 weeks in Ekso. Both groups showed statistically significant improvement in gait speed and walking distance. Statistically significant improvements were also found for lower extremity strength and

ambulatory function in both groups, and for home/community ambulation in the sub-acute group.[32] Finally, 5 out of 12 walked overground at baseline in the sub-acute group, whereas 9 walked at endpoint; 4 out of 11 walked overground at baseline in the chronic group, whereas 7 walked at endpoint.[32] Preliminary data for acute inpatients with multiple diagnoses (n=6, mostly stroke), with mean days since diagnosis of only 16 days and half initially unable to complete the 10MWT, has shown average gait speed improvements after a mean of 7.3 ± 2.3 sessions with a mean of 416 ± 194 steps.[11] These improvements surpassed the MCID (0.16 m/s) and limited community walking threshold (0.40 m/s) for stroke[34] at 0.18 m/s and 0.44 m/s, respectively.[11] FIM transfer and locomotion scores also increased significantly.[11]

Ekso and Balance

Human balance, or postural control, is the ability to "maintain, achieve, or restore [one's] line of gravity within [one's] base of support" to prevent a fall.[35] The balance measures BBS and TUG are highly correlated to walking in spinal cord injury (SCI) and stroke ($|r| = 0.81$-0.93).[36-39]

Several studies have shown that training in Ekso improves balance outcome measures in these diagnoses. A total of 11 participants with incomplete SCI, as well as those with complete SCI, decreased their time on the TUG while in the device, suggesting improved balance while supported by the exoskeleton.[17,19] Outside of the device, significant improvements in TUG in incomplete SCI (n=4)[28] and in trunk control in stroke[32] have been reported. Although not statistically significant, Flaherty et al.[11] reported an average improvement of over 5 inches in the Functional Reach Test outside the device (n=6).

The authors of the PanEuro study noted that the device relies on proper weight shifting to take the next step, and that training weight shifts should in turn train balance. Ramanujam et al.[20,23] tracked the center of mass of participants with SCI during walking in Ekso (n=3), showing closer and more symmetric stability around midline[20], as well as "improved control …of weight shifts and balance" after both high and low dosage training (n=7, range 3-100 hours).[20,23] These combined changes demonstrated "a more efficient weight transfer strategy" and "improved dynamic stability", resulting in a significant improvement in gait speed in the device. Motion capture in 5 participants with stroke showed weight shifts to be more centered with better symmetry of steps, while EMG showed more normal, distinctive lower extremity muscle bursts from the user.[13] Improved midline alignment and excursion during standing outside the device after 4 weeks of training suggests better static stability as well.[40] Further studies of control of weight shifting during standing and walking are recommended, incorporating EksoGT's SmartAssist software with real-time standing balance visual and audio feedback. This more normal gait pattern, more centered static and dynamic postures, enhanced strength, and higher dosage may enhance functional outcomes capacity during rehabilitation.

While the improvements in these outcome measures show increased *capacity* to walk, they do not necessarily translate into walking *activity* outside of the clinic. Low self-efficacy, or poor confidence to perform or complete a task successfully, has been studied as a limiting factor for walking post injury. French et al.[41] studied 59 participants at least 6 months post stroke, finding that walking capacity results

significantly predicted self-efficacy results (Walk 12, Activities-Specific Balance Confidence (ABC) Scale, and Functional Gait Assessment (FGA)) and that self-efficacy results predicted walking activity and participation results. However, walking capacity results did not significantly predict walking activity or participation results. They determined that self-efficacy "mediated the relationship of performance-based [factors] with activity and participation" and suggest including self-efficacy measures in research and rehabilitation. In a similar study, in 55 participants at least 3 months post stroke, Danks et al.[42] determined that a person's walking capacity only explained 36% of the variability in his/her walking activity. A significant portion of the remaining variability was explained by 1) self-efficacy during balance tasks (ABC Scale) and during walking (Walk 12), and 2) the interaction of the ABC with the FGA. The statistical tests showed that balance self-efficacy was a significant predictive factor of walking activity and "moderated the relationship between walking capacity and walking activity". The authors stressed that increasing self-efficacy through successes during rehabilitation may not only improve walking capacity, but also increase walking activity after discharge, thereby decreasing the secondary sequelae of immobility.

Ekso and Secondary Complications

Ekso has been reported to ameliorate a myriad of secondary complications following SCI and stroke, as well as increase quality of life. Two studies have shown significantly increased muscle volume and reduced intramuscular fat in chronic SCI (n=13).[26,43] Lower extremity strength (n=28+)[21,26,32,44] and bone density (n=6)[43,44] have also been shown to improve after SCI and stroke. Participants have reported significantly reduced pain (n=18)[14,18,19,44,45] and pain medication use (n=2)[14,44] and reduced spasticity (n=32),[8,14,21,45,46] after SCI, with some having trained 1-3x/wk for 5-20 sessions, but about half having walked in Ekso for only one session.[46] Participants with SCI have also reported improved bowel and bladder function (n=~18)[14,21,44,46,47] and improved sleep (n=5).[14,18] Preliminary data have so far shown 36 sessions of exoskeleton training (of which Ekso was one) reduced risk for cardiovascular disease via increased HDL cholesterol (n=~4), although LDL cholesterol, total cholesterol, nor triglycerides changed.[48] Notably, participants with SCI have reported significantly improved quality of life after 18 sessions (n=20).[27] Four participants with stroke reported they were more positive and motivated about their recovery when using Ekso.[49] Participants with SCI have reported improved mood and motivation (n=6)[21], as well as reduced depression and improved body image (n=13)[50] with Ekso training. Users of Ekso with SCI have also described the psychological benefits of being upright and walking: appreciation of upright interactions with others, reduced anxiety and anger, and feelings of control, accomplishment, hope (n=8)[51] and "a positive vision of the future" (n=13).[50]

Ongoing Studies and Future Directions

The company-sponsored Walking Improvement for Spinal Cord Injury in Exoskeleton (WISE) randomized controlled trial began in 2016. Ten sites are included in this study to determine the effectiveness of a training protocol (3x/wk for 12 weeks) with EksoGT and SmartAssist software on gait, secondary complications, and PT and participant burden as compared to standard physical therapy for those with incomplete SCI. A similar RCT has begun in stroke this year with several participants already enrolled. Other ongoing studies include outcomes in walking, energy expenditure, and cognition in participants

with MS; bowel, bladder, muscle, and bone changes in SCI; blood flow changes in stroke and SCI; and psychological impact in multiple neurological diagnoses. A new, multi-center safety and feasibility study has just been launched to include deconditioned participants, whether in acute or long-term care rehabilitation. Using EksoGT and SmartAssist software, additional research is sought into changes in postural control and balance during walking, especially in those with midline alignment impairment and "pusher" syndrome after stroke.

Combining therapies often results in improved outcomes. Researchers at UCLA combined transcutaneous spinal cord stimulation (tSCS) with Ekso gait training for 5 sessions in one person with complete SCI to successfully evoke volitional lower extremity movement (outside of the device), perspiration, and cardiovascular control.[52] Further study of adding tSCS and Busprione with Ekso training showed increased muscle activity and improved coordination patterns.[53] Brain stimulation before or during Ekso training via transcranial direct current (tDCS) or magnetic field (TMS) may be another way to augment outcomes. Despite the intervention, assessments of brain activity (EEG) and/or muscle activity/motor control (EMG) will be critical to future studies to show neuroplastic changes in the brain and spinal cord. We must understand these mechanisms underlying functional changes and relate them to participant characteristics of responders and non-responders to optimize EksoGT's use in neurorehabilitation.

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