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2

3 **An MRI compatible loading device for the reconstruction of clinically relevant plantar**
4 **pressure distributions and loading scenarios of the forefoot**

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13 **Keywords:** Weight bearing MRI, Plantar pressure, tissue deformation, diabetic foot, joint
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28 **Abstract:**

29 This study aims to present a new MRI compatible loading device capable of reconstructing realistic
30 loading scenarios of the human foot for research in the field of foot biomechanics. This device has
31 two different configurations: one used to compress the forefoot and one to bend the
32 metatarsophalangeal joints. Required plantar pressure distribution under the metatarsal heads can be
33 achieved by modifying the distribution of the dorsally applied forces. To validate the device, subject-
34 specific plantar pressures were measured and then reconstructed using the device. For quiet stance the
35 peak pressure reconstruction error was 3% while for mid-stance phase of gait it was 8%. The device
36 was also used to measure the passive bending stiffness of the metatarsophalangeal joints of one
37 subject with low intra-subject variability. A series of preliminary MRI scans confirmed that the
38 loading device can be used to produce static weight-bearing images of the foot (voxel size:
39 0.23mm×0.23mm×1.00mm).

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41 The results indicate that the device presented here can accurately reconstruct subject specific plantar
42 pressure distributions and measure the foot's metatarsophalangeal passive stiffness. Possible future
43 applications include the validation of finite element models, the investigation of the relationship
44 between plantar pressure and internal stresses/strains and the study of the foot's inter-segmental
45 passive stiffness.

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56 **1. Introduction**

57 Investigating the internal stresses and strains of the human foot soft tissues is crucial to the
58 understanding of foot biomechanics [1,2]. The significance of internal tissue stress and strain is even
59 more pronounced in the case of the diabetic foot. Previous research indicates that ulceration begins
60 internally and could be caused by deep tissue trauma [3]. In this context a number of different
61 methodologies have been developed for the direct measurement of internal strains using medical
62 imaging [2,4–12]. These protocols usually involve a comparison of an unloaded image of the tissue's
63 structure against the images of the loaded structures under a range of externally applied loads. The
64 implementation of this concept requires a method with three main constituents: a medical imaging
65 modality, a tissue-loading device and an algorithm/procedure to quantify and map the changes of the
66 tissues' structure [10].

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68 From the common imaging modalities Magnetic Resonance Imaging (MRI) appears to be the most
69 suited one for a detailed analysis of the three dimensional (3D) field of internal deformations of soft
70 tissues [2]. MRI offers a superb contrast for the imaging of soft tissues and it doesn't employ any
71 ionizing radiation. However, one of the main disadvantages of using MRI is the fact that applying
72 loads in a controlled and repeatable manner inside an MRI scanner is considerably more difficult
73 compared to other available modalities such as ultrasonography [4], fluoroscopy [5,6] or computer
74 tomography (CT) [7–9]. The use of MRI imposes a number of limitations in terms of the dimensions
75 and the materials that can be used to build a loading device, hence a number of studies have looked at
76 tackling this challenge for various anatomical regions [2,13].

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78 To investigate the internal deformations of the foot, Petre et al. [2] developed a sophisticated MRI
79 compatible loading device capable of applying both normal and shear loads to the forefoot. The
80 pilot testing of this device indicated that despite its capacity to apply "gait-like loading" [2] it couldn't
81 generate plantar pressure distributions similar to the ones measured during walking. This was
82 attributed to the fact that the loading device simultaneously applied a net force to both the metatarsal
83 head (MTH) and toe regions and there was no control over the distribution of the load [2].

84

85 In contrast to internal deformations, the internal stresses of plantar soft tissues cannot be directly
86 measured, but they can be estimated with the use of finite element (FE) models [1,10]. An accurate
87 3D FE model of the foot though, requires a large amount of information on its internal structure and
88 the mechanical properties of its soft tissues (i.e. skin, fat, muscle etc.). Furthermore to accurately
89 replicate realistic loading scenarios such models need information on the function and stiffness of its
90 numerous joints and they have to be validated against experimental data.

91

92 The bending stiffness of joints in general can be analysed in two components: a dynamic one
93 associated with active muscle forces and a passive one associated with the elastic properties of non-
94 contractile tissues [14]. Hence measuring the passive stiffness of the joints of the foot in addition to
95 enhancing our understanding on their function it can also give clinically relevant information about
96 the mechanical status of non-contractile tissues, such as ligaments, tendons etc.

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98 In this context the present study aims to present a novel MRI compatible device for the accurate
99 reconstruction of subject specific plantar pressure distributions of the forefoot and the simulation of
100 clinically relevant loading scenarios. This device was designed and built to enable the study of the in-
101 vivo mechanical behaviour of the plantar soft tissues of the forefoot under compression as well as for
102 the study the mechanical behaviour of the passive foot under bending.

103

104 **2. Participants and methods**

105 A total of six healthy volunteers (4 female, 2 male) with an average age of 33.0 (± 6.3) years and
106 average body mass of 70.9 (± 7.7) kg were recruited for this study (Table 1). Ethical approval was
107 sought and granted by the University Ethics Committee and the volunteers provided full informed
108 consent.

109

110 The MRI compatible loading device was designed using SolidWorks[®] 2010 (Dassault Systèmes, Paris,
111 France). The device consisted of custom made parts milled from polypropylene blocks and connected

112 with Nylon plastic screws and bolts. The device (Figure 1) has a fixed part (A) for foot support and a
113 movable one (B) for loading. The movable part (B) can rotate around a predefined axis (C). The
114 device can be configured so that the initial angle between part B and the plantar surface of part A is
115 either 90° or 0°. Each one of these two configurations enables the application of different load
116 scenarios (compression or bending modes respectively). In both cases the loading is applied with the
117 help of a suspended MRI compatible mass. The suspended mass can be up to 5 Kg which generates a
118 maximum compressive force of ≈ 250 N or bending moment of ≈ 7 Nm. During the design of the
119 loading device special attention was paid to minimize its dimensions and make sure it will fit inside a
120 typical MRI scanner with a bore aperture of 60 cm [15].

121

122 **2.1 Compression mode**

123 The loading device is capable of applying known compressive forces at the dorsal side of the forefoot.
124 For this purpose the movable part B (Figure 1A) is positioned at 90° with respect to the foot-support
125 (A) and equipped with a compression punch (D). This punch is used to compress the forefoot and to
126 control the distribution of the applied load. More specifically a series of screws is used to modify the
127 profile of the contact area between the punch and the dorsal surface of the foot (Figure 1A). The
128 relative position of the foot and punch can also be modified with the use of 5 mm thick plastic sheets
129 (E). Positioning the compression punch at the dorsal side of the MTHs enables the controlled loading
130 of the soft tissues that lie directly below them. When a compressive load is applied at the dorsal side
131 of the forefoot these non-contractile soft tissues (mainly skin and fat) are compressed between the
132 foot-support (A) and the MTHs.

133

134 The ability of this device to reconstruct subject specific plantar pressure distributions was assessed in
135 a pilot study. More specifically the loading device was used to reconstruct the plantar pressure
136 developed at the MTH region during quiet stance and the mid-stance phase of walking gait.

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138 The quality of the MRI images that can be recorded when the foot is under the static weight bearing
139 conditions generated by the device was assessed in a series of preliminary scanning sequences. The

140 forefoot region of a volunteer was compressed with a net force of 250 N and imaged using a 1.5 T
141 MRI scanner. The duration of the scanning process was \approx 4 min and coronal T1 weighted 3D Fast
142 Field Echo (FFE) images (Figure 2) were recorded with in-plane and out of plane resolution of 0.23
143 mm and 1.00 mm respectively. No plantar pressure measurement was performed inside the MRI
144 scanner.

145

146 **2.1.1 Quiet stance**

147 In the case of quiet stance the average peak pressure under each Metatarsal Head (MTH) was
148 measured for each of the six volunteers using a plantar pressure sensor (F-scan®, Tekscan, Boston,
149 MA, US) (Figure 1A). The volunteers stood on the sensor and the area under each MTH was
150 identified by applying pressure manually at the dorsal side of the foot. The relative location of each
151 MTH on the pressure sensor was utilized to measure the peak plantar pressure of each MTH (Figure
152 3). The plantar pressure was recorded at a sampling rate of 100 Hz for 10 sec of quiet stance and the
153 average peak pressure for each MTH was calculated to produce the reference measurements for the
154 reconstruction. The relative position of the foot and the sensor was fixed using double sided tape. The
155 volunteers' feet were then placed inside the loading device and a pressure was applied at the dorsal
156 side of their forefoot. The suspended mass was gradually increased (in increments of 0.5 Kg) to
157 approximate the total forefoot force. The profile of the punch was sequentially modified starting from
158 the MTH with the maximum reference pressure and then moving medially and laterally to reconstruct
159 the pattern of the reference plantar pressure distribution. This procedure was repeated until the
160 difference between the reference and the reconstructed peak pressures was less than 5%. After
161 achieving a satisfactory replication of the overall pattern of pressure distribution, the plantar pressure
162 was recorded again for 10 seconds at a sampling rate of 100 Hz. One additional pressure measurement
163 was performed for a single participant (participant #6) with the compression punch completely flat
164 (i.e. before any modification of its profile) to highlight the versatility of the loading device.

165

166 The duration of loading was decided based on preliminary results indicating that the plantar pressure
167 distribution generated by the loading device stays practically constant for long periods of time. More

168 specifically a net compressive force of 150 N was applied to the forefoot of a volunteer and the peak
169 plantar pressure was recorded at 1 Hz for 20 minutes of continuous loading. The average value and
170 standard deviation of the peak pressure was calculated.

171

172 The reproducibility of the results was assessed through a test re-test procedure (Table 1). After
173 completing all tests, the loading procedure and pressure measurements were repeated for one
174 volunteer (#5) without reconfiguring the loading device (i.e. the suspended mass and the profile of the
175 compression punch was the same for both test and re-test).

176

177 **2.1.2 Mid-stance phase of gait**

178 In the case of the mid-stance phase of gait the plantar pressure of a complete gait cycle was recorded
179 for a single volunteer (#5) using a walkway pressure mapping system (Walkway®, Tekscan, Boston,
180 MA, US). An automated procedure within the Walkway® system was used to identify the area below
181 each MTH and to measure the corresponding pressure in each region. In this case the reference values
182 for the reconstruction procedure were the peak pressures under the MTHs for a randomly selected
183 instance of the mid-stance phase of gait (50% of mid-stance). The plantar pressure developed inside
184 the loading device was measured again using F-scan®.

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186 **2.2 Bending mode**

187 Reconfiguring the loading device allows the application of known bending moments to the foot. For
188 this purpose parts A and B are positioned parallel to one another and the compression punch is
189 removed (Figure 1B). In this configuration a rotation of part B around its axis (C) tends to bend the
190 subject's foot instead of compressing it. The relative position of the foot with respect to the rotation
191 axis can be modified with the use of 5 mm thick plastic sheets (E) (Figure 1B). These sheets are
192 placed between the foot and the foot's support elevating the foot along two axes: one parallel and one
193 perpendicular to the plantar surface (Figure 1B). When the device is used inside an MRI scanner the
194 relative angle between parts A and B can be measured from the MRI images.

195

196 The bending mode of the MRI compatible loading device was pilot tested for a single volunteer by
197 measuring the bending stiffness of the metatarsophalangeal (MP) joints. For this purpose the bending
198 axis of the volunteer's MP joints was first identified based on anatomical landmarks [16]. The
199 volunteer's foot was fixed inside the device using Velcro straps (Figure 1B) and using a goniometer
200 the bending angle of the MP joints was measured for bending moments ranging from 1.8 Nm to 4.5
201 Nm. Ten preconditioning load/unload cycles were performed before each measurement and each
202 measurement was repeated five times.

203

204 **3. Results**

205 **3.1 Compression mode**

206 The pilot MRI scan indicated that the quality of the MRI images recorded when the foot is under the
207 static weight bearing conditions generated by the device have a resolution that is high enough to
208 enable the identification and segmentation of different tissues of the foot (Figure 2).

209

210 **3.1.1 Quiet stance**

211 In the case of quiet stance the average difference between the reference and the reconstructed total
212 maximum pressures was only 4% while the mean difference for all MTHs ranged between 2% and
213 15% (Table 1). In all cases the total maximum pressure was observed under the same MTH for both
214 the reconstructed and the reference pressure distributions. As it can be seen in Table 1 and Figure 3
215 the loading device was capable of reconstructing different and distinctive subject specific loading
216 patterns. The ability of the device to modify the distribution of plantar pressures becomes clearer if
217 one compares the initial pressures that are measured in the device before any adjustment of the
218 compression profile (i.e. for a compression profile that is completely flat) to the final ones after all
219 necessary adjustments had been completed (Figure 3).

220

221 Moreover the loading device was capable of maintaining a constant distribution of plantar pressure for
222 long periods of time. The average peak pressure measured for 20 minutes of continuous loading was
223 equal to 111.8 kPa with a standard deviation of only 4.3 kPa (i.e. 3.8% error). In terms of

224 reproducibility, the test-retest procedure yielded differences in terms of average peak pressures that
225 were lower than 5% (Table 1).

226

227 **3.1.2 Mid-stance phase of gait**

228 In the case of mid-stance phase of gait the average difference between the reference peak pressures
229 and the reconstructed average peak pressures was 8% (Table 1). The difference between the overall
230 maximum values was also 8%.

231

232 **3.2 Bending mode**

233 The standard deviation of the measured rotation angles for different values of the externally applied
234 moment was always lower than 3 deg indicating a relatively low intra-subject variability (Table 2).
235 Moreover, bending angle appeared to increase linearly with moment ($R^2=0.98$). The slope of the
236 moment/angle graph was equal to 0.06 Nm/deg.

237

238 **4. Discussion**

239 The purpose of this study was to present a new foot loading device that is capable of reconstructing
240 clinically relevant loading scenarios inside an MRI scanner. This device was initially designed to
241 enable the validation of 3D FE models of the foot and more specifically to help assess their accuracy
242 to predict the internal stresses and strains of plantar soft tissues and to simulate the function of the
243 foot's joints. For this reason a custom made device was designed to allow two different configurations
244 for the application of different loads, i.e. compression and bending. Having two different
245 configurations for compression and bending enabled the realisation of different loading scenarios
246 using a single device instead of two while at the same time helped simplifying the design of the
247 device.

248

249 The new method for the reconstruction of subject specific pressure distributions presented here was
250 focused on the MTH area. The MTH area along with the heel and the hallux are the areas with the
251 highest ulceration rates in people with diabetes. A recent study by Ledoux et al. [17] demonstrated for

252 the first time that the ulceration risk for the MTH area is correlated to in-shoe peak plantar pressure.
253 No similar correlation was found for the heel and hallux which could indicate that in the case of the
254 MTH area ulceration is caused by normal loading instead of shear while in the case of the heel and
255 hallux shear loading (among other reasons) could be the main risk factor. These results highlight the
256 importance of studying the in-vivo mechanical behaviour of the plantar soft tissues of the MTH area
257 and the clinical relevance of analysing their internal strain fields with the help of medical imaging.

258

259 There are two ways to load the forefoot inside a typical MRI scanner: either by supporting the dorsal
260 side of the passive foot and loading the plantar one [2] or by supporting its plantar side and loading its
261 dorsal one. Considering that pressure is developed at both sides of the foot regardless of the direction
262 of the externally applied load, it becomes clear that the deformations of the dorsal soft tissues will
263 always be unrealistic. Indeed these tissues are not normally meant to be subjected to large
264 compressive loads. On the other hand the plantar soft tissues of the MTH area are compressed
265 between the plantar surface of the loading device and the MTHs. This compressive load within the
266 internal structures will be generated regardless of the direction of the external load either from the
267 dorsal or the plantar aspect of foot. In addition, this scenario closely simulates the loading conditions
268 of quiet stance and the mid-stance phase of gait. The only way to validate the accuracy of this
269 reconstructed internal loading condition is with the help of upright weight bearing MRI, which is
270 beyond the scope of this manuscript.

271

272 In a previous attempt to simulate clinically relevant loading scenarios inside an MRI scanner Petre et
273 al. [2] developed a loading device that was capable of applying “gait-like loading” [2] but couldn’t
274 reconstruct subject specific plantar pressure distributions. According to the results presented by Petre
275 et al. [2], the average difference in terms of peak pressure between the reference and the reconstructed
276 loading was 66% while only in 50% of the cases the reconstructed peak pressure was observed under
277 the correct MTH (i.e. the same MTH as in the reference pressure distributions) [2]. This was
278 attributed to the lack of control over the distribution of the load and to the fact that the device applied
279 a net force simultaneously to both the MTH and toe regions [2].

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In order to address this issue the device presented here was equipped with a specially designed punch. This punch is used to compress the forefoot and modify the distribution of the applied load. This unique feature allowed the accurate reconstruction of diverse and distinctive subject specific plantar pressure distribution patterns. Indeed the average difference between the reference and the reconstructed maximum pressures was only 4% and in every case the maximum pressure was observed under the same MTH for both the reconstructed and the reference pressure distributions. Based on these results it can be concluded that the device presented here offers a clear improvement for the reconstruction of subject specific plantar pressure distributions of the MTH area.

The reproducibility of loading with an accuracy of 5% that was assessed through a test-retest procedure allows the reconstruction of subject specific loading conditions inside an MRI scanner. This allows configuring the device before entering the MRI environment with the use of pressure measurement sensors that are not usually MRI compatible and then to reproduce the same loading conditions inside the scanner.

Another challenge stems from the fact that MRI scanning can be a rather lengthy process and therefore loading should be kept constant for a significant amount of time. The device presented here was proven capable of keeping loading constant for up to 20 minutes (net force= 150 N, average peak pressure = 111.8 kPa). Even though the results indicated that even higher loads could be sustained for even longer periods of time the actual limits both in terms of loading and time is more likely to be set based on considerations about the comfort and wellbeing of the subject rather than the capabilities of the device. With respect to this, special attention needs to be given to patients with impaired circulation and nerve damage to prevent trauma. Considering the limited access to the device inside the MRI scanner special care should be given to ensure that the toes of the subject are kept in a neutral position and that the skin at the dorsal side of the foot is not over-stretched as a result of loading.

307 The second configuration of the device allows the application of bending moments. Even though this
308 loading scenario does not simulate an everyday activity it can give clinically relevant information on
309 foot biomechanics. Imaging the foot under bending loads can shed light on the function of the joints
310 of the foot and the stiffness of their non-contractile tissues, like ligament and tendon stiffness, with
311 implications in assessing the functional impairment in conditions like diabetes.

312

313 In the context of this study the bending stiffness of the MP joints of one subject with no known
314 musculoskeletal abnormality or diabetes was measured for validation and demonstration purposes. As
315 expected, the passive bending stiffness of the MP joints measured here was significantly lower
316 compared to measurements taken during locomotion. Oleson et al.[16] studied the stiffness of the
317 forefoot during running with the use of a motion analysis system. They concluded that the MP joints
318 have a time-dependend stiffness and its function resembles that of an “active mechanism” instead of a
319 linear spring [16]. The bending stiffness reported by Oleson et al. [16] was close to 1.6 Nm/deg for a
320 flexion angle of 20 deg while the respective value of the passive stiffness measured here was only
321 0.06 Nm/deg.

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323 No specific conclusions can be drawn on the mechanical behavior of the MP joints at this point due to
324 the nature and design of this pilot investigation. Although the bending tests were performed on a
325 single subject, further studies will use this device to measure the passive MP joint stiffness of people
326 with no musculoskeletal abnormalities or diabetes as well as of people with diabetes to study
327 differences in terms of joint mobility and stiffness. Previous investigations indicate that people with
328 diabetes are often found to have limited joint mobility which is linked to increased ulceration risk
329 [19]. Increased joint stiffness caused by non-enzymatic glycosylation is presumed to be one of the
330 main contributors of limited joint mobility of the diabetic foot’s distal joints [19]. Studying the
331 passive bending stiffness and the mobility of the joints within the diabetic foot will shed light on the
332 causative factors of this pathological change with the potential to help improve current therapeutic
333 approaches for the reduction of ulceration rates.

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336 The type and range of loading scenarios that can be realised using this device is mainly limited by the
337 fact that in its current form it cannot apply combinations of different types of loading such as
338 compression and bending or combined compression and shear. For this reason the plantar pressure
339 reconstructions performed here were limited to load cases where shear loads are minimal such as quiet
340 stance and the mid-stance phase of gait. Despite this limitation the device could be used with minor
341 modifications to study loading scenarios involving compression of the forefoot at different
342 dorsiflexion angles of the toes. The dorsiflexion angle of the toes could be modified easily with the
343 use of wedges with different inclinations. Another limitation of this device is that it cannot be used to
344 study rate dependent phenomena.

345

346 For the purposes of the present study the maximum compressive force applied to a subject was 250 N.
347 Even though this force may seem relatively low compared to the net forces applied to the foot during
348 everyday activities the results of this study indicate that if this force is properly focused it can
349 generate plantar pressures in order of magnitude that are relevant to the cases of quiet stance and mid-
350 stance phase of walking gait. The maximum net compressive force that can be applied by the device
351 is mainly limited by the fact that pressure is applied on a relative small area at the dorsal side of the
352 foot. Because of that increased loads could cause discomfort or trauma. Even though the simulation of
353 loading scenarios involving higher compressive forces at the MTH area (i.e. similar or higher than
354 body weight) were beyond the scope of this study, minor modifications could increase the magnitude
355 of the compressive force that can be safely applied. Increasing the contact area between the
356 compression punch and the dorsal side of the foot would allow the application of significantly higher
357 forces.

358 The MRI compatible loading device presented here can realise clinically relevant loading scenarios
359 and allows the accurate reconstruction of subject specific plantar pressure distributions of the MTH
360 area for the cases of quiet stance and mid-stance phase of gait. The device can be used to validate
361 numerical models of the foot, where the loading is applied by a virtual punch. The validated foot
362 models can then be used to simulate real-life scenarios. In the future this device can be used for the

363 investigation of the correlation between plantar pressure and internal tissue stresses and strains as well
364 as for the study of the forefoot's inter-segmental passive stiffness.

365

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370 footwear using an integrated approach and Smart materials.

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373 **Competing interests:** None declared

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457 **Tables**

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459 Table 1: The reference and the reconstructed average peak pressures measured under each MTH for
 460 the case of quiet stance (six volunteers) and the respective reference peak pressures and reconstructed
 461 average peak pressures (one volunteer) for the case of mid-stance phase of gait. The overall maximum
 462 values for each volunteer are highlighted.

		Quiet stance						Mid-stance	
		#1	#2	#3	#4	#5 <i>Test</i>	#5 <i>Re-test</i>	#6	#5
Volunteer:									
Gender (M/F):		F	M	F	M	F	F	F	F
Age (y)		32	35	45	38	30	30	24	30
Weight (Kg):		60	82	72	82	67	67	70	67
Max. Pressure (kPa)	1st Reference/	29/	176/	46/	69/	218/	218/	50/	57/
	MTH Reconstructed	26	163	46	70	221	211	58	65
	2nd Reference/	70/	60/	79/	64/	66/	66/	51/	97/
	MTH Reconstructed	78	67	82	64	64	70	69	97
	3rd Reference/	51/	88/	95/	60/	77/	77/	77/	98/
	MTH Reconstructed	52	90	91	57	42	46	76	106
	4th Reference/	53/	167/	57/	49/	49/	49/	41/	91/
	MTH Reconstructed	53	151	80	50	40	42	35	85
	5th Reference/	42/	184/	61/	68/	37/	37/	37/	92/
	MTH Reconstructed	41	185	62	66	35	38	38	81
Mean error (%):		5	6	10	2	15	15	14	8

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465 Table 2: The results from the pilot testing of the device's bending mode. The bending angle values of
 466 all five trials are presented.

Bending moment (Nm)	Bending angle (deg)					Average	STDEV
	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5		
1.8	89	90	90	90	90	90	0
2.2	105	99	103	103	103	103	2
3.3	120	120	119	119	124	120	2
3.9	126	123	127	127	127	126	2
4.6	133	138	139	140	138	138	3

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469 **Figure legends:**

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471 Figure 1: Two different configurations of the MRI compatible loading device used to apply
472 compressive (A) and bending loads (B). The punch used to apply the compressive load and to control
473 its distribution is also shown.

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475 Figure 2: MRI images of the forefoot before (A) and after compression (B). The boundaries of the
476 foot and of the visible bones have been manually outlined for both cases (dotted blue and continuous
477 red curves for A and B respectively) and presented together (C) for comparison.

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479 Figure 3: The reference planar pressures (left) and the ones measured inside the device before (centre)
480 and after (right) the adjustment of the compression punch profile for volunteer #6 (pressure in kPa).
481 The area of the MTHs is defined using a number of polygons. Inside each one of these polygons the
482 location of peak pressure is marked by a rectangle. The average values of the peak pressures of each
483 MTH are also plotted together for comparison.

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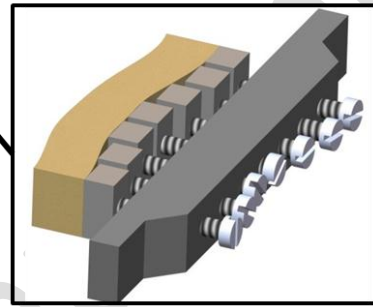
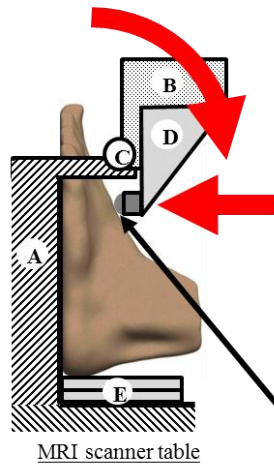
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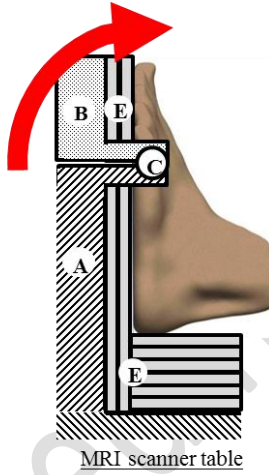
497 Figure 1:

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(A)



(B)



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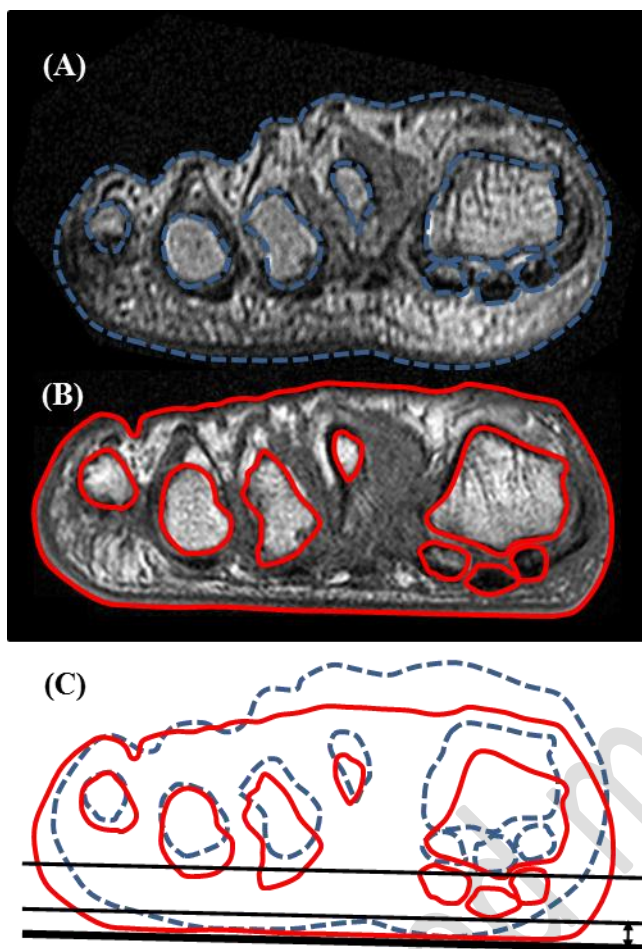
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511 Figure 2:

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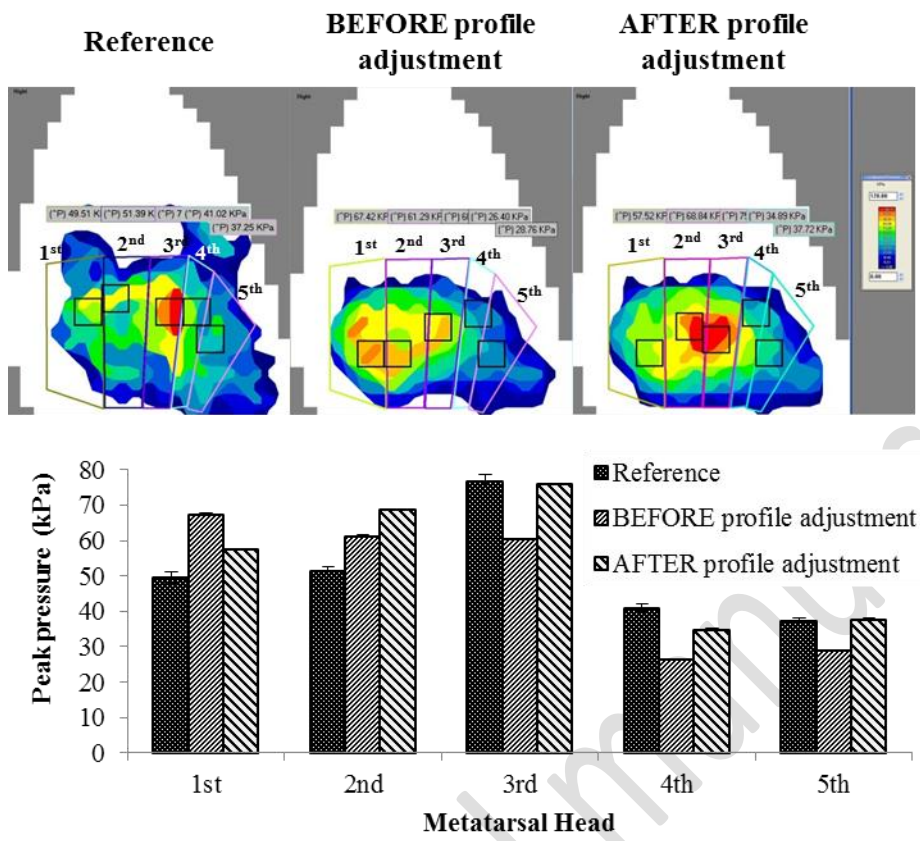
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525 Figure 3:

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