

Investigating the influence of intermittent and continuous mechanical loading on skin through non-invasive sampling of IL-1 α

J.F.J. Soetens^{a,b,*}, P.R. Worsley^{a,b}, D.L. Bader^{a,b}, C.W.J. Oomens^{a,b}

^a Eindhoven University of Technology, Department of Biomedical Engineering, Eindhoven, the Netherlands

^b Southampton University, Faculty of Health Sciences, Southampton, United Kingdom

ABSTRACT

Pressure ulcers (PUs) are a major burden to both patients, carers and the healthcare system. It is therefore important to identify patients at risk and detect pressure ulcers at an early stage of their development. The pro-inflammatory cytokine IL-1 α is a promising indicator of tissue damage. The aim of this study was to compare the temporal skin response, by means of IL-1 α expression, to different loading regimens and to investigate the presence of individual variability. The sacrum of eleven healthy volunteers was subjected to two different loading protocols. After a baseline measurement, the left and right side of the sacrum were subjected to continuous and intermittent loading regimen, respectively, at a pressure of 100 mmHg. Data was collected every 20 min, allowing for a total experimental time of 140 min. Sebum, collected at ambient conditions using Sebutape, was analyzed for the pro-inflammatory cytokine IL-1 α . Most robust results were obtained using a baseline normalization approach on individual data. The IL-1 α level significantly changed upon load application and removal ($p < 0.05$) for both loading regimens. Highest IL-1 α ratio increase, 3.7-fold, was observed for 1 h continuous loading. During the refractory periods for both loading regimen the IL-1 α levels were still found to be up-regulated compared to baseline ($p < 0.05$). The IL-1 α level increased significantly for the two initial loading periods ($p < 0.05$), but stabilized during the final loading period for both loading regimens. Large individual variability in IL-1 α ratio was observed in the responses, with median values of 1.91 (range 1.49–3.08), and 2.52 (range 1.96–4.29), for intermittent and continuous loading, respectively, although the differences were not statistically significant. Cluster analysis revealed the presence of two distinct sub-populations, with either a low or high response to the applied loading regimen. The measurement after the first loading period proved to be representative for the subsequent measurements on each site. This study revealed that trends in normalized IL-1 α provided an early indicator for tissue status following periods of mechanical loading and refractory unloaded conditions. Additionally, the observed individual variability in the response potentially identifies patients at risk of developing PUs.

1. Introduction

Pressure ulcers (PUs) are defined by the National and European Pressure Ulcer Advisory Panel (2014) as “a localized injury to skin and/or underlying tissue, usually over a bony prominence, as a result of prolonged mechanical loading in the form of pressure, or pressure in combination with shear”. External pressure and shear forces will result in internal tissue deformations, resulting in two major damage mechanisms that are involved in the development of PUs [14]. Firstly, ischemic damage caused by the occlusion of blood- and lymph vessels which occurs at relatively low internal strains. The resulting deficiency of vital nutrients and accumulation of toxic metabolites lead to tissue damage, a process which takes several hours to develop. Alternatively, direct cell damage resulting from high internal strains, a process that can occur within minutes.

Clinical prevention strategies currently focus on pressure relief via periodic repositioning and pressure redistribution [13]. To aid clinical decision making, pressure mapping technologies have been used to monitor pressure redistribution and movement patterns [10]. However,

the predictive power of these measures is limited due to the variability of tissue tolerance to pressure magnitude and duration [16]. Indeed the individual tissue tolerance is an intrinsically determined property, which depends on various risk factors such as immobility, skin status and comorbidities [3,8]. Despite major efforts in developing effective preventative measures, prevalence values of PUs remains high ranging between, for example, 10%–42% in intensive care units [4]. Therefore additional research is needed in order to develop new strategies for the prevention and early detection of PUs.

Ideally, preventive measures are tailored to the tissue tolerance of individuals at risk. A promising strategy to monitor the tissue status involves the use of noninvasive biomarkers. For example the pro-inflammatory cytokine IL-1 α was reported to be up-regulated over category I pressure ulcers [2]. Moreover, the IL-1 α expression was significantly increased upon skin loading [1,6] and, more recently, was reported to be sensitive to monitor the skin response when subjected to both pressure and shear [7]. In addition, with respect to device-related PUs, IL-1 α was elevated with increasing loading duration on spine boards [11], strap tension of ventilation masks [19] and cervical collars

* Corresponding author. Groene Loper, Building 15, Room 4.11, P.O. Box 513, 5612AZ, Eindhoven, the Netherlands.

E-mail address: j.f.j.soetens@tue.nl (J.F.J. Soetens).

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[20]. Altogether this makes IL-1 α a promising candidate for early PU formation.

This study was designed to compare the temporal skin response to different loading regimens and to investigate the presence of individual variability in this response. This was achieved by subjecting a cohort of healthy volunteers to both intermittent and continuous loading at the sacrum and monitoring the temporal skin response, by means of the pro-inflammatory cytokine IL-1 α .

2. Materials and methods

2.1. Participants

The participants were recruited from the local university population. The protocol was approved by the ethics committee of University of Southampton (ERGO-FOHS-19647), and informed written consent was obtained from the participants before testing and for the publication of the images.

2.2. Test equipment

The sacrum was selected as the test site as it is relatively flat and one of the more common areas for pressure ulcers. Loading of the sacrum was achieved through a custom made loading device, designed to be compatible with the used standard hospital bed. Two independent cylindrical weights (1.4 kg, ϕ 36 mm) were lowered onto each side of the sacrum, resulting in an equivalent pressure of 100 mmHg (13.3 kPa). Assessment of the physiological response of the skin was achieved by collecting sebum from the skin surface using Sebutape (CuDerm, Dallas, TX, USA), following an optimized protocol based on that of Perkins et al. [15].

2.3. Test protocol

Testing was performed at ambient laboratory conditions controlled at a temperature of $20 \pm 2^\circ\text{C}$ and relative humidity of $40 \pm 5\%$. Each participant remained as still as possible in a prone position on a standard viscoelastic hospital mattress. The measurement sites, left and right sacrum and lower back were then identified and cleared of clothing. Each site was subjected to a different loading regimen (see Fig. 1).

The session started with a 20 min acclimatisation period during which all three sites remained completely unloaded, providing baseline values for each measurement site. The left and right side of the sacrum were subsequently subjected to continuous and intermittent loading, respectively (Fig. 2). The continuous loading regimen involved three loading periods of 20 min, followed by three unloading periods of 20 min. By contrast, the intermittent loading regimen consisted of three consecutive cycles of 20 min loading followed by 20 min unloading. The lower back served as an adjacent unloaded control. Including baseline

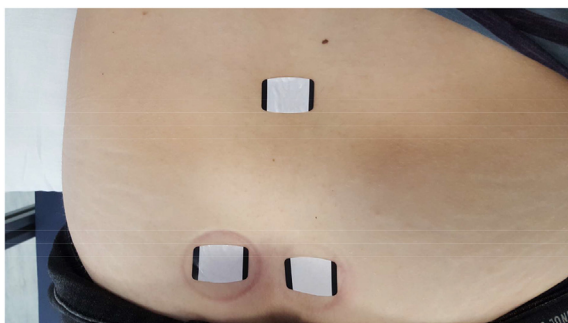


Fig. 1. Sebutapes were used to collect sebum from each of the three measurement sites, left and right sacrum and lower back, respectively.

measurement, this allowed for a total experimental duration of 2 h and 20 min. During the final 2 min of each period Sebutape measurements were performed (Fig. 2) which, in the case of the two loading sites, necessitated the removal of the load briefly to ensure Sebutape placement. Directly after the test period, the Sebutape samples were coded and stored at -80°C prior to analysis.

2.4. Biochemical analysis

The adsorbed proteins were extracted from the Sebutape following an optimized protocol based on Perkins et al. [15]. To review briefly, the Sebutapes were placed in 2 mL of phosphate buffered saline (PBS, Sigma-Aldrich Co., St. Louis, MO, USA) with the addition of 0.05% TWEEEN20 (Sigma-Aldrich Co., St. Louis, MO, USA), a non-ionic detergent that enhanced the protein recovery from the tapes. The tubes were placed for 1 h on a roller mixer and were then sonicated for 10 min at room temperature. Subsequently they were individually vortexed for 2 min and mixed with a sterile pipette tip before analysis.

The concentration of IL-1 α was determined by the Multiplex Core Facility of the Laboratory for Translational Immunology at the University Medical Center Utrecht. Measurements were performed using an in-house developed and validated (ISO9001 certified) multiplex immunoassay (Laboratory of Translational Immunology, University Medical Center Utrecht) based on Luminex technology (xMAP, Luminex Austin TX USA). The assay that was performed, as described previously by Scholman et al. [17], is highly sensitive to the detection of IL-1 α , with a limit of detection (LOD) of 0.6 pg/mL, and a lower and upper limit of quantification (LLOQ and ULOQ) of 2.1 and 5051.4 pg/mL, respectively.

Additionally, total protein (TP) concentration in the Sebutape samples was determined using a colorimetric Micro BCA Protein Assay Kit (Product No. 23235, Thermo Fisher Scientific, USA), which enabled correction for sebum uptake during each measurement period [7,11].

2.5. Data analysis

Statistical analysis was performed using IBM SPSS Statistics V23 (IBM Corporation, Armonk, NY, USA). Measured absolute IL-1 α concentrations were normalized to baseline values from each specific site. Normality was assessed using the Shapiro-Wilk test. Due to small sample sizes, pairwise comparisons were tested for significance using the non-parametric Wilcoxon signed rank test. The presence of distinct sub-populations in the data was investigated using a Two Step cluster analysis. Data is presented using median (interquartile range) for non-normally distributed data. The statistical significance level was set at $p < 0.05$.

3. Results

3.1. Participants

Eleven healthy participants (7 males and 4 females) were included in the study with a mean age of 32 years (range 21–65 years). Their mean height was 1.73 ± 0.08 m and mean weight was 74.5 ± 10.8 kg with a corresponding body mass index of 24.8 ± 2.5 kg/m². Two participants were excluded from the analysis since the measured baseline concentration of IL-1 α was below the LLOQ.

3.2. IL-1 α analysis

Large individual variability in the absolute concentrations of IL-1 α was observed both at baseline and in the response to loading of the sacrum, as illustrated with the intermittent loading for two participants in Fig. 3a and b. Therefore, in order to combine and compare individuals, the IL-1 α ratio was calculated from each measurement site by normalization to baseline, see Fig. 3c and d.

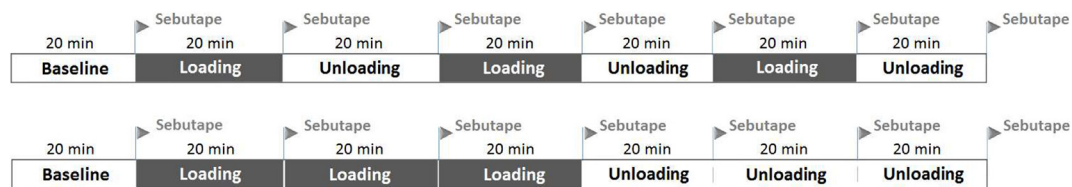


Fig. 2. Timelines of the experimental protocol, with intermittent (top) and continuous loading (bottom) regimen applied to the right and left side of the sacrum, respectively. Each regimen consists of 7 periods of 20 min, in which either loading (grey) or no loading (white) was applied. The final 2 min of each period were used for Sebutape sampling.

Table 1 provides a summary of the outcome data, both absolute and normalized IL-1 α levels are given, for the control, intermittent and continuous loading regimen, respectively. The IL-1 α ratio on the back, the unloaded control site, does not significantly change over time compared to baseline as shown with the Wilcoxon signed rank test ($Z = -1.400$ to -0.208 , $p = 0.161$ to 0.779). This implies that any significant change in IL-1 α ratio found on the sacrum could be attributed to the applied loading regimen.

It was evident that the mean IL-1 α ratio corresponds to the applied regimen for both intermittent and continuous loading (Fig. 4). A significantly elevated expression is observed after loading and load removal results in significant recovery of the mean IL-1 α levels, as exemplified in the intermittent response (all $p < 0.05$). It is noted that the highest increase in IL-1 α ratio was observed with continuous loading, with a mean ratio of 3.6 (Fig. 4b).

Although load application results in an enhanced response, the increase stabilizes during the last loading period for both loading regimens. The differences in IL-1 α ratio compared to baseline remain statistically significant during the three unloading periods, for both intermittent ($p = 0.021$, 0.062 and 0.04) and continuous ($p = 0.06$, 0.013 and 0.041) loading as revealed using the Wilcoxon rank sign test. This prolonged elevation of the response indicates that the duration of intermittent load removal involving a 20 min period is insufficient to return to baseline levels of IL-1 α .

A further analysis of individual data involved estimating the mean accumulated response during the first 2 h of measurement and enabled comparison of the effects of both intermittent and continuous loading (Fig. 5). This revealed individual variability in the IL-1 α response for

both loading regimens.

Indeed the response to continuous loading with median 2.52 (1.96–4.29) was higher than for intermittent loading with 1.91 (1.49–3.08). Due to variance in the response across the participants, these differences were not statistically significant ($Z = -1.423$, $p = 0.155$). Comparison on an individual basis, however, shows that three individuals demonstrate a strongly elevated response to continuous loading compared to intermittent loading (Fig. 6a).

Using a Two Step cluster analysis, two distinct sub-populations were found in the response to continuous loading, with mean values of 2.0 ± 0.73 and 4.3 ± 0.58 . Similar analysis of the response to intermittent loading again revealed two distinct sub-populations, with mean values of 1.57 ± 0.29 and 3.20 ± 0.53 . All is shown in Fig. 6b. Eight of the eleven individuals belonged to the same, low or high response, sub-population for both intermittent and continuous loading (coloured areas, Fig. 6b). Three individuals belonged to different sub-populations for both loading regimens.

Further analysis of the individual data examined whether the measured up-regulation of IL-1 α ratio after the first loading period (L1) was representative of the accumulative response, as illustrated in Fig. 7. Using the non-parametric Spearman's rank correlation test it is shown that the response to intermittent loading is significantly reflected in the up-regulation after the first loading period with $\rho = 0.964$ ($p = 0.001$). In a similar manner for continuous loading, the normalized up-regulation after the first loading period is indicative of the total response with $\rho = 0.727$ ($p = 0.011$).

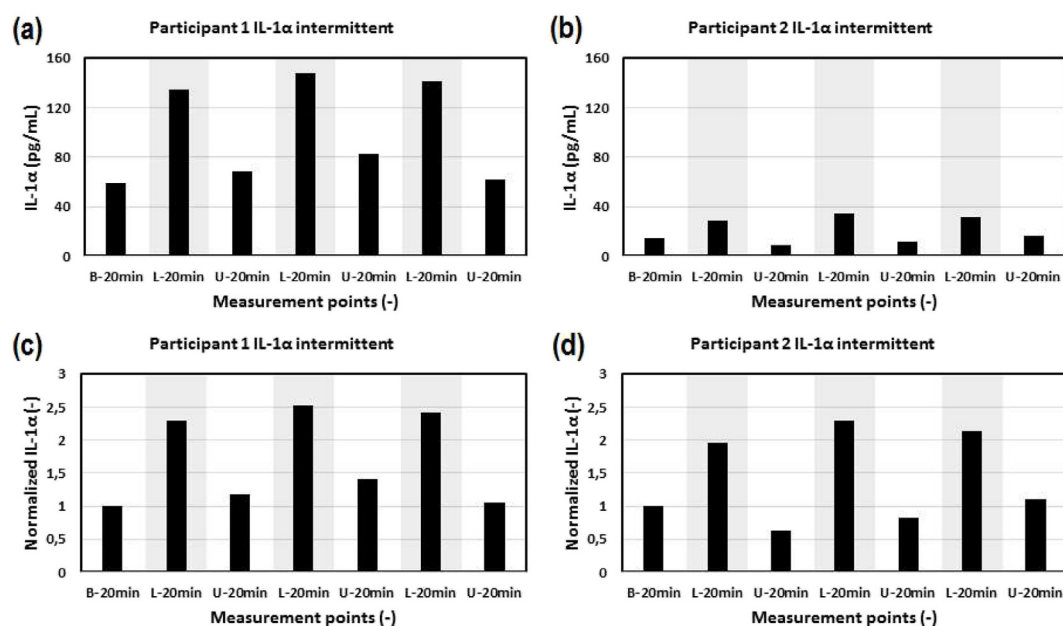


Fig. 3. The response to intermittent loading for two participants in terms of normalization of absolute IL-1 α concentrations (a,b) and baseline (c,d). Grey background depicts periods of loading.

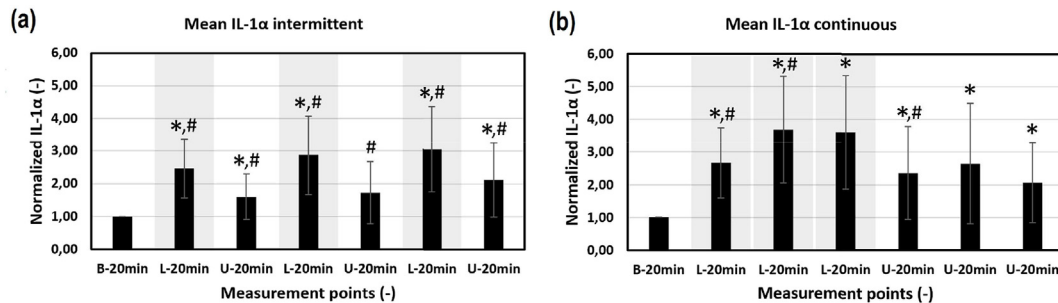
Table 1

Summary of outcome measure data for control, intermittent and continuous loading regimen, presented in median (interquartile range).

Control		Intermittent		Continuous	
Absolute IL-1 α (pg/mL)	Normalized IL-1 α (-)	Absolute IL-1 α (pg/mL)	Normalized IL-1 α (-)	Absolute IL-1 α (pg/mL)	Normalized IL-1 α (-)
B1 87.4 (31.0–219.4)	1.00 (1.00–1.00)	BL 38.5 (22.5–58.7)	1.00 (1.00–1.00)	BL 35.1 (23.9–37.2)	1.00 (1.00–1.00) ^a
B2 78.1 (3.9–126.1)	0.80 (0.57–1.29)	L1 81.9 (29.2–135.2)	2.30 (1.77–3.51) ^{a,b}	L1 82.5 (66.2–108.0)	2.52 (1.96–3.36) ^{a,b}
B3 89.8 (27.5–137.8)	0.84 (0.50–1.28)	U1 58.0 (31.2–90.6)	1.59 (1.05–2.12) ^{a,b}	L2 136.3 (55.6–191.5)	3.72 (2.32–4.33) ^{a,b}
B4 94.7 (45.3–162.2)	0.89 (0.75–1.67)	L2 100.2 (39.4–148.5)	2.53 (1.76–3.67) ^{a,b}	L3 110.8 (52.0–141.1)	3.47 (2.89–4.23) ^a
B5 101.7 (34.0–189.2)	0.77 (0.64–1.61)	U2 77.7 (12.1–97.4)	1.70 (0.82–2.51) ^b	U1 54.7 (39.7–110.2)	1.66 (1.43–3.83) ^{a,b}
B6 64.3 (31.0–139.9)	0.96 (0.52–1.30)	L3 107.1 (37.8–155.7)	3.02 (1.92–3.94) ^{a,b}	U2 53.8 (28.5–133.6)	1.53 (1.17–4.74) ^a
B7 87.9 (41.5–135.9)	1.12 (0.86–1.41)	U3 62.0 (35.1–112.1)	1.50 (1.10–2.87) ^{a,b}	U3 62.7 (18.7–93.3)	1.71 (0.93–3.52) ^a

Notes: ^a Significant difference ($p < 0.05$) between current value and BL. ^b Significant difference ($p < 0.05$) between current and previous value.

Abbreviations: B = back; BL = baseline; L = loading; U = unloading.

**Fig. 4.** Mean IL-1 α response for all participants to both intermittent (a) and continuous (b) loading regimen. Presented data is mean \pm standard deviation. Grey background depicts period of applied loading. * significant difference between current value and baseline. # significant difference between current and previous value.

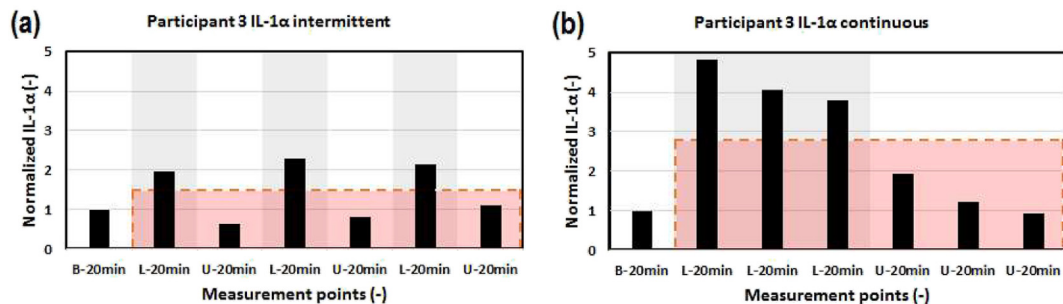
4. Discussion

This study was designed to compare the temporal differences in the expression of a specific pro-inflammatory cytokine when the skin at the sacrum was subjected to either intermittent or continuous loading regimens. Previously an up-regulation of the pro-inflammatory cytokine IL-1 α was reported over category I pressure ulcers [2]. The current study revealed IL-1 α as a potential indicator of skin status as its expression corresponded to both applied loading regimens. Indeed loading of the sacrum caused a significant up-regulation of IL-1 α , whereas removal of the load resulted in partial recovery of the expression level.

The IL-1 α ratio was determined from each of two measurement sites by normalization to baseline. This approach has also been recently adopted by Worsley et al. [19,20] and allowed for robust analysis for both the mean and individual measurements. By contrast, other studies [7,11] normalized absolute IL-1 α to total protein (TP) concentration, which, in the present study, resulted in inconsistency in the individual results. Based on the current findings it can be stated with confidence that the preferred approach involves longitudinal measurements with baseline normalization.

In the present study the temporal release of IL-1 α is monitored during both loading and recovery phases, as opposed to previous studies which only investigated the IL-1 α response pre- and post-loading [7,19,20]. Current findings revealed a mean 3.7-fold up-regulation after an hour of continuous loading, which is of similar magnitude (2.4–5.8 fold) to that reported when cervical collars were applied at different strap tensions [20]. Hemmes et al. [11] investigated the temporal release of IL-1 α on the sacrum of healthy volunteers during loading and subsequent recovery in a clinically relevant setting using different spineboards. In concordance with their findings, the present study shows an initial significant increase in IL-1 α levels during the first two loading periods, although there was no subsequent change during the final loading period (Fig. 4b). This may suggest that the onset of tissue damage is more likely to occur as a result of an accumulated temporal up-regulation of IL-1 α , as opposed to a value in excess of a defined threshold.

It is also clear that during unloading recovery periods, the IL-1 α levels remained elevated compared to baseline levels (Fig. 4a). Similar findings were reported by Hemmes et al. [11], where 1 h after load removal the IL-1 α /TP ratio remained significantly increased. This indicates that although the mechanical stimulus is removed, there is a

**Fig. 5.** The mean accumulated response (outlined area) of one individual participant during the final 2 h of measurement to both intermittent (a) and continuous (b) loading regimen. Grey background depicts period of applied loading.

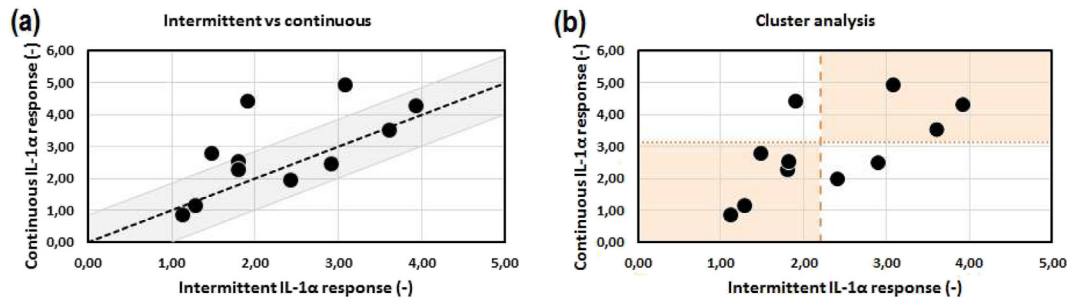


Fig. 6. (a) Comparison between the individual response to intermittent and continuous loading regimen, with the dotted line (standard deviation in grey) indicating a similar response. (b) Results of the Two Step cluster analysis, indicating the presence of 2 distinct sub-populations to both intermittent and continuous loading. Low and high response to intermittent loading are located left and right of dashed line, respectively. Low and high response to continuous loading are located below and above the dotted line, respectively. Points in the coloured areas belong to the same sub-population, low or high response, for both intermittent and continuous loading regimen.

refractory period required for the inflammatory cytokines to return to baseline levels. In the intermittent loading regime of the current study, consecutive reapplication and removal of the load also had an accumulative effect on the IL-1 α level (Fig. 4a). The exact implications of this prolonged elevation in IL-1 α level on the evolution of tissue damage remains unknown and is worthy of investigation in future studies.

Quantification of the individual response was performed by calculating the mean IL-1 α ratio during the 2 h loading regimen. No significant difference was found in IL-1 α expression between intermittent and continuous loading regimen on the sacrum (Fig. 6). It is interesting to note that similar findings were reported by Loerakker et al. [12], where the evolution of skeletal muscle damage in an animal model was investigated due to either intermittent (12 \times 10 min) or continuous loading (120 min). Intermittent tissue relief did not appear to demonstrate a significant effect on the evolution of tissue damage which, due to the time scale of the experiment, was restricted to direct mechanical deformation damage in the absence of ischemic-related damage. As shown by Stekelenburg et al. [18], the induction of complete ischemia by a tourniquet for 2 h did not induce significant tissue damage. This implies that the influence of intermittent load relief on the evolution of ischemic tissue damage, and thus expression of IL-1 α , does not play a significant role in the current study with a total loading duration of 1 h on each site. The benefit of intermittent load relief could be assessed by elongation of the current experimental loading regimen to over 2 h.

There is a large variability observed in the participant-specific responses to both loading regimens. This is indicated by the range of IL-1 α ratios observed in the response to both intermittent (1.13–3.94) and continuous (0.86–4.93) loading (Fig. 6a). Similar variability was reported by Worsley et al. [20] and analyzed in more detail by Cornelissen [5]. Using a Two Step cluster analysis, they observed the presence of two distinct sub-populations in the IL-1 α response to 100 mmHg applied for 2 h at the volar forearm. One cluster had a mean IL-1 α release of 2.00 ± 0.49 , while the other revealed a high elevated mean of 4.20 ± 0.53 . Although the sample size in the current study is limited

($N = 11$), a similar analysis reveals the presence of two distinct sub-populations in the continuous loading regimen, with means of 2.00 ± 0.73 and 4.30 ± 0.58 . Similarly, the response to intermittent loading revealed the presence of two distinct sub-populations with means of 1.57 ± 0.29 and 3.20 ± 0.53 , respectively. Comparison of both sub-populations showed eight participants with similar, low or high, response to both applied loading regimens, while three participants were in different sub-populations for both loading regimens (Fig. 6b). Individual demographic factors did not explain the observed variability. This approach therefore needs further investigation with more participants. Nevertheless, the variability in the response is potentially indicative for the individual susceptibility to PU development and the current findings could assist in identifying patients at risk.

The individual data reveals three individual participants who demonstrated an enhanced response to continuous loading when compared to intermittent loading. Close examination of the data reveals that this is due in part to the relatively low baseline levels of IL-1 α measured at the continuously loaded site. The levels of IL-1 α ratio reached during continuous loading are therefore 2–3 times higher than during intermittent loading, leading to a significantly increased mean response. These findings reveal the high sensitivity to the single baseline measurement at each site and therefore highlights an effective limitation of the current experimental protocol. In addition, two participants were excluded due to baseline measurements below the lower LOQ of the currently used detection method. Both issues can be overcome by performing multiple baseline measurements at each site.

This study also does not account for the influence of the ischemic damage process in the tissue. In order to gain more insight in the ischemic process, measurements could be combined with metabolic markers, such as lactate and pyruvate. Indeed Hemmes et al. [11] reported that, although ischemic damage was not an issue in their specific time frame, significant differences in lactate concentration could be measured due to 1 h of sacral loading. This implies that lactate is a suitable indicator for tissue ischemia. Monitoring both the mechanical

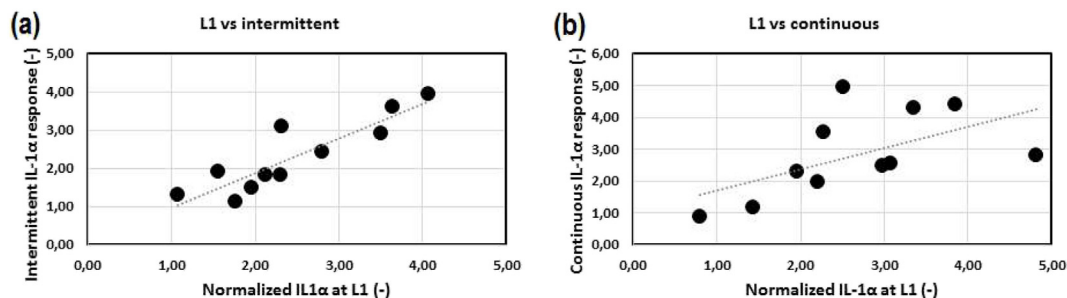


Fig. 7. Comparison between the determined individual response to both intermittent (a) and continuous (b) loading and the measured IL-1 α ratio after the first loading period (L1).

and ischemic damage processes for each individual provides additional information which might, in turn, explain the observed individual variability in the response to loading and thereby help in assessing the individual susceptibility for PU development.

From a clinical perspective, performing a measurement of over a 2 h period to determine the individual susceptibility may prove impractical. This motivated the analysis of IL-1 α levels measured after 20 min of loading (L1) as a predictor of the total response of each participant. This resulted in a significant correlation between L1 and the total response (Fig. 7) for both the intermittent ($\rho = 0.964$) and continuous loading regimen ($\rho = 0.727$). This implies that the individual response to mechanical loading of the sacrum can be determined within a relative short amount of time and could be used in the clinic to identify patients at risk.

The present study was performed on a cohort of healthy volunteers. However, it is well established that the inflammatory response can be influenced by a plethora of intrinsic and extrinsic factors, complicating the extrapolation of the currently adopted test method. As an example chronic inflammation, representing a common co-morbidity in spinal cord injured, obese or elderly individuals will inevitably result in temporally elevated levels of inflammatory markers. By contrast the use of medication, such as corticosteroids, suppresses the inflammatory response. The altered inflammatory state caused by these factors potentially affects the individual tolerance to tissue loading [8]. The precise effects of these factors on the expression of inflammatory biomarkers requires further investigation, particularly when considering those sub-groups of individuals at risk of developing PUs.

A point-of-care biosensor that is capable of continuous measurement of IL-1 α level expressed at the skin surface remains a promising tool for the early detection of pressure ulcers. Moreover, it could be implemented in existing preventative measures, such as prophylactic wound dressings [9]. Ideally such a biosensor would require of continuous tissue monitoring capability with high sensitivity, features which demand further innovations in sensor technology. Current findings, however, show the potential of IL-1 α as a biomarker for the early detection of pressure ulcers and potential indicator for patients at risk of developing PUs.

5. Conclusions

This study revealed that trends in normalized IL-1 α provided an early indicator of tissue status following periods of mechanical loading and refractory unloaded conditions. No significant differences were found between the responses to intermittent and continuous loading. Large variability was observed in the participant-specific response to both intermittent and continuous loading, potentially indicating the individual susceptibility to PU development. The individual response to the applied loading regimen could be significantly predicted with the measured IL-1 α level after the first 20 min loading period.

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