Title page

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Title

An individually moulded insole with 5-mm medial arch support reduces peak impact and loading at the heel after a one-hour treadmill run

Abstract

Background: Foot pain experienced by long-distance runners could be relieved by functional insoles which aim at evenly distributing the plantar pressure.

Research question: We hypothesised that an individually moulded insole with medial arch support would reduce the impact and loading under the heel and metatarsal regions.

Methods: Twelve male recreational runners ran on a treadmill at 10 km/h for 1 hour with flat insoles and medial arch supported insoles. A pressure insole system (Novel Pedar, Germany) was used to obtain the peak pressure, peak force, time normalised pressure-time integrals, and the percentage of the total force-time integrals under 10 regions.

Results: Medial arch supported insoles reduced the peak force under the heel (medial: -15.3%, $p = 0.001$; lateral: -19.2%, $p = 0.037$) during the initial run, and reduced peak pressure under the heel (medial: -13.3%, $p = 0.005$; lateral: -9.9%, $p = 0.006$), and peak force under the medial heel (-17.8%, $p = 0.006$) after the run. The percentage of the total force-time integrals under the heel was reduced (medial: -23.8%, $p = 0.004$; lateral: -13.6%, $p = 0.022$) after the run. No significant difference was found under the metatarsal regions. There is shift of load from the metatarsal regions to the medial mid-foot as indicated by the change of the percentage of total force-time integrals.

Significance: Medial arch supported insoles were effective in reducing the impact and loading under the heel region in prolonged running on a treadmill.

Level of evidence: Controlled laboratory study, Level V

Keywords: orthosis, footwear, gait, insert, foot

Introduction

Long-distance running has become increasingly popular over the past 50 years [28]. Despite its health benefits on reducing body fat [20], resting blood pressure [8], cardiovascular disease, and mortality risk [11], it is also associated with chronic musculoskeletal conditions such as medial tibial stress syndrome, Achilles tendinopathy, and plantar fasciitis [12]. Plantar foot pain occurs mainly in the forefoot under the metatarsal heads [7] and the heel [25] and is believed to be caused by an excessive load from repetitive impact to these regions [29]. During an endurance or exhaustive run, when muscle fatigue occurs, there is an increased loading to the metatarsal and midfoot regions [2,19]. These are possible reasons for foot pain occurrence in both heel and forefoot regions, and this load may also cause metatarsal bone deformation and metatarsal stress fracture [1].

There were two explanations proposed for the increase in loading under the metatarsal region. The first explanation, proposed by Nigg [21], was the change of foot contact pattern during fatigued running. He suggested that during fatigued running, the foot contact pattern changed from heel-toe to midfoot-toe. In heel landing, a plantarflexion moment is produced about the ankle which must be counteracted by eccentric contraction of the tibialis anterior. However, if the tibialis anterior is fatigued, the heel landing strategy would change to a mid-foot landing strategy, so a dorsiflexion moment will be created rather than a plantarflexion moment to unload the tibialis anterior. As a result, the load under the heel will be transferred to the mid-foot or metatarsal region. The second explanation, proposed by Willson and Kernozek [30],

1 was the flattening of the medial longitudinal arch of the foot. They proposed that
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3 during fatigued running, muscles such as the tibialis posterior that supports the medial
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5 longitudinal arch may fail to function. The foot then becomes ‘flat foot’ during the
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7 stance phase of running. As a result, the loading under the mid-foot region and
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9 metatarsal region may become higher.
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14 There are many functional shoes and insert designs for cushioning [24], under both
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16 the heel region [26] as well as the metatarsal or forefoot region [6]. There is also a
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18 belief that for shoes to be comfortable, it is better to distribute the body weight as
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20 evenly as possible on the plantar surface [4]. The concept to distribute the body
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22 weight evenly under the whole plantar region in a pair of shoes is called ‘footbed’
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24 [31]. There are also custom-made functional insoles for foot comfort during running
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26 [15]. However, the cost can be 4-5 times more expensive (£137.65) than
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28 off-the-shelf prefabricated insoles (£31.73) as it may involve individualised 3D
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30 scanning and printing. Moreover, the effect of these custom-made insoles is also not
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32 always superior, even in people with foot problems [24]. Prefabricated insoles are
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34 mainly designed to increase medial arch support to fill the hollow space beneath the
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36 medial midfoot. This is intended to maximise the entire plantar area of contact to
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38 distribute the pressure [5]. Although they are suggested to be more cost-effective for
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40 running [13], there is no proof for the effect in evenly distributing the plantar
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42 pressure.
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53 Thus, an individually moulded insole with medial arch support can be considered as
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55 an intermediate option. The personalised prescription may better help distribute
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57 plantar pressure during running than a prefabricated insole, and is less expensive
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59 compared with custom-made functional insoles which involve 3D scanning and
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printing. This study investigated the effect of an individually moulded insole with medial arch support on plantar pressure and force distribution during a one-hour treadmill run. We hypothesised that the individually moulded insole with medial arch support would reduce the impact (as indicated by peak pressure and peak force) and loading (as indicated by the percentage of the total force-time integrals) under (1) the heel, and (2) the metatarsal regions.

Method

Sample size estimation was done in G*Power software (Germany), based on a previous study, which reported the mean peak pressure under the medial foot before and after a 40-minute run at 10-12 km/hr to be 107.74 ± 31.98 kPa and 104.80 ± 26.53 kPa with the participants' original shoes and insoles as control, and to be 76.48 ± 24.20 kPa and 71.13 ± 18.51 kPa with the original insoles replaced by prefabricated insoles for even plantar pressure distribution in running [14]. Mean peak pressure under the medial foot was chosen as the key parameter as the purpose of the prefabricated insoles was to fill the hollow space under the medial foot for an evenly distributed plantar pressure. Thus, a change on the pressure under this region is expected. By setting the level of significance to 0.05 and the statistical power to 0.80 in a two-tailed test for matched pairs, between the control and prefabricated insoles before and after the run, the effect size was calculated to be 1.082 and 1.323, and the estimated required sample size was calculated to be 9 and 7 respectively.

Twelve male recreational runners (Age: 38.5 ± 8.0 years, height: 176.0 ± 5.5 cm, body mass: 62.6 ± 4.3 kg) participated in this study. They were all right-footed with foot length between 255-260 mm and normal foot arch as indicated by an arch index between 0.21-0.26 [16], and were free of injury in the previous year. All participants

1 were engaged in regular running activities for at least 20 km per week and were
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3 required to stop running for at least one day before the experiment. All participants
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5 signed written informed consent, and the study was approved by the Joint Chinese
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7 University of Hong Kong – New Territories East Cluster Clinical Research Ethics
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9 Committee.
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14 A pair of running shoes (Mizuno, Japan, Size 260 mm) was provided for all
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16 participants. The original insole of the running shoe was removed and replaced by two
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18 different insoles: (1) a flat insole without any arch support (Control), made by 5 mm
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20 thickness insole material (ethylene vinyl acetate), and (2) an insole with medial arch
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22 support, individually moulded from each participant's positive foot cast, with an extra
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24 5mm thickness of ethylene-vinyl acetate added underneath the medial arch as
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26 reinforcement (Figure 1). The moulding process was performed by the same certified
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28 prosthetic and orthotic specialist. Based on the 3D shape of the positive foot cast,
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30 individually moulded insoles matching each participant's foot shape and medial arch
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32 height were fabricated. The highest point over the medial arch was about 10 mm.
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34 Each participant performed two running tests with the two insoles, with the two
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36 sessions being at least two weeks apart. In each test, participants first ran for about 5
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38 minutes as a warm-up with self-selected speed, which was gradually increased to 10
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40 km/h when the one-hour main trial started, followed by another 5-minute cool-down
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42 with the speed gradually slowed down to zero.
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53 A pressure insole system (Novel Pedar model W, Munich, Germany) was used to
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55 record the distribution of plantar pressure. There were 99-sensors embedded in the
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57 insole with 100 Hz sampling frequency. The insole was divided into 10 anatomical
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59 regions, which were automatically masked by the system as medial heel (M01), lateral
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1 heel (M02), medial mid-foot (M03), lateral mid-foot (M04), 1st metatarsal head
2 (M05), 2nd and 3rd metatarsal heads (M06), lateral metatarsal heads (M07), hallux
3 (M08), 2nd and 3rd toes (M09) and lateral toes (M10) as shown in Figure 2. Peak
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heel (M02), medial mid-foot (M03), lateral mid-foot (M04), 1st metatarsal head (M05), 2nd and 3rd metatarsal heads (M06), lateral metatarsal heads (M07), hallux (M08), 2nd and 3rd toes (M09) and lateral toes (M10) as shown in Figure 2. Peak plantar pressure, time normalised pressure-time integrals, peak force, and percentage of the total force-time integrals were evaluated in each region. Ten steps after the initial 5 minutes of the main trial (initial run) and the last 10 steps before the end of the main trial (final run) were collected and analysed. Menz [17] stated that analysing both feet in foot and ankle research could generate spurious or false-positive results and suggested that the simplest way around the problem is to select one side to analyse. Therefore, in this study, data from only the right foot (dominant foot, which was verbally reported by the participants as the preferred limb to kick a ball) were analysed, by the in-built software with the pressure insole system.

Statistical Analysis

The dependent variables were the peak plantar pressure, time normalised pressure-time integrals, peak force, and the percentage of the total force-time integrals in 10 plantar regions. Shapiro-Wilk test was performed to check normality. If normality was achieved (e.g. $p > 0.05$), a two-way multivariate analysis of variance (insole x time) with repeated measures (MANOVA) was applied on the plantar pressure parameters to show any significant effects by insole and time. If an interactive effect of insole and time was found, post hoc stratified paired t-tests were performed to demonstrate the insole effect at each time point (initial run and final run), as well as the time effect for each insole (flat and arch supported). If an interactive effect was not found, t-tests on each main effect (insole/time) were performed. If normality was not achieved, the parametric procedures were replaced by the corresponding non-parametric procedures, e.g. Friedman MANOVA and stratified

U-tests. Statistical significance level was set at $p < 0.05$ level. All statistical analysis procedures were performed with statistical analysis software (SPSS 16.0, IBM Corporation, Armonk, NY, USA).

Results

Shapiro-Wilk test suggested that normality was achieved. MANOVA with repeated measures showed significant interactive (insole x time) effect ($p < 0.05$), therefore, stratified paired t-tests were performed. The mean values and standard deviations of all dependent variables in the initial run and final run for two insoles are shown in Table 1. During the initial run, peak force under the medial heel (M01) and lateral heel (M02) was lower with the medial arch supported insole ($p < 0.05$). During the final run, peak pressure under the medial heel (M01), lateral heel (M02) and medial mid-foot (M03), peak force under the medial heel (M01), and the percentage of the total force-time integrals under the medial heel (M01) and lateral heel (M02) were lower with the medial arch supported insole ($p < 0.05$). The percentage of the total force-time integrals under the 2nd and 3rd metatarsal heads (M06) was higher with the medial arch supported insoles ($p = 0.013$).

In comparing the difference between the initial run and the final run, a significant increase was found in many of the dependent variables for both flat insoles and the medial arch supported insole. The increase of peak pressure and peak force were mainly on the heel and midfoot (M01-M04). The increase of time normalised pressure-time integrals was found in all ten regions (M01-M10). The percentage of total force-time integrals dropped mainly in metatarsal heads regions (M05-M07) for both insoles and shifted to the medial heel (M01) and the toes (M9-M10) for flat insoles and medial mid-foot (M03) for medial arch supported insole ($p < 0.05$).

Discussion

This study hypothesised that the individually moulded insole with medial arch support would reduce the impact (as indicated by peak pressure and peak force) and loading (as indicated by the percentage of the total force-time integrals) under (1) the heel, and (2) the metatarsal regions. The data suggested the first part of the hypothesis was confirmed, as the individually moulded insole with medial arch support reduced the peak force under the heel (medial heel, M01: from 194.6 N to 164.9 N, % change = -15.3%, $p = 0.001$; lateral heel, M02: from 360.3 N to 291.2 N, % change = -19.2%, $p = 0.037$) during the initial run, and reduced peak pressure under the heel (medial heel, M01: from 250.0 kPa to 216.8 kPa, % change = -13.3%, $p = 0.005$; lateral heel, M02: from 255.8 kPa to 230.5 kPa, % change = -9.9%, $p = 0.006$), and peak force under the medial heel (M01, from 228.6 N to 187.9 N, % change = -17.8%, $p = 0.006$) after the one-hour treadmill run. Loading at the medial heel was reduced as indicated by a percentage drop of the total force-time integrals (medial heel, M01: from 8.4% to 6.4%, % change = -23.8%, $p = 0.004$; lateral heel, M02: from 13.2% to 11.4%, % change = -13.6%, $p = 0.022$) after the run. The second part of the hypothesis is rejected, as no significant reduction in any parameter was found under the metatarsal regions (M05-07). Nevertheless, a significant increase in the percentage of the total force-time integrals was found under the 2nd and 3rd metatarsal heads (M06, from 15.4 to 17.2%, % change = +11.7%, $p = 0.013$) after the run.

Functional insoles, inserts, orthoses, or orthotics have been prescribed for people with different conditions. Twenty years ago, the main purposes of these prescriptions were mainly for reducing impact force and controlling foot pronation [22]. Many biomechanics studies have been conducted to demonstrate the effect of different shoe

1 insoles or modifications on cushioning, stability, and balance [9]. Since 2015, Nigg
2 and colleagues [23] proposed two new paradigms, namely ‘preferred movement path’
3 and ‘comfort filter’, and suggested that runners would select comfortable products
4 using their own comfort filter that allows them to remain in the preferred movement
5 path. Nowadays, more studies have focused on plantar pressure distribution [3], as
6 many researchers believe that comfort is achieved by evenly distributing the plantar
7 pressure under the entire plantar surface. These devices have also been prescribed to
8 people with different musculoskeletal or medical conditions, such as plantar fasciitis
9 [10] medial tibial stress syndrome [18] knee osteoarthritis [32], etc.

24 For some patients with diabetes, functional shoes, and inserts are thought to be
25 essential as the patients need to avoid local high pressure under certain plantar regions
26 of their feet to avoid the development of ulcers [24]. However, a recent review
27 suggested that while custom-made orthoses are not always more effective than
28 prefabricated orthoses, the higher cost makes the clinical effectiveness and
29 cost-effectiveness questionable [27]. For recreational runners, it seems like there is no
30 need to use custom-made insoles for more even plantar pressure distribution. The
31 moulded insole with medial arch support in this study was not costly; each pair
32 costing only about USD 10. In this study, although no reduction of mean peak
33 pressure under the metatarsal regions was found, there was also not a significant
34 increase. The values for the flat and arch supported insoles ranged from 203.1-256.7
35 kPa and 207.3-264.8 kPa respectively. If forefoot cushioning is also desired,
36 metatarsal pads or forefoot cushioning orthosis can be added [6].

57 In this study, no significant reduction in the impact and loading under the metatarsal
58 regions were found. A possible reason was that the added medial arch support simply
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was not effective. Another possible reason was that in the stance phase during running, the impact peak at early stance happens mainly under the heel, and the propulsive peak later in the stance happens mainly under the metatarsal regions. Many shoe designs were for reducing the impact peak at early stance under the heel [22] as this repetitive impact force was believed to be harmful. The propulsive peak at the late stance happens under the metatarsal regions. It is essential for pushing off the ground for propagation and therefore it cannot be reduced [26]. Therefore, this may explain why the peak pressure and peak force under the metatarsal regions stayed the same, or else the participants would be unable to propagate off the ground and complete the running task. The reduction of peak impact at the heel could be explained by the load shared by the medial mid-foot region (M03). This effect may not show in peak pressure and pressure-time integrals as they concern only the value of one sensor with the highest recorded value. The rest of the sensors in that region are disregarded. If the load is transferred to other foot regions, they can be shown by greater force-time integrals. The percentage of the total force-time integrals under the medial mid-foot (M03) was 9.1% for the flat insole and was 10.6% for the individually moulded insole with medial arch support (% change = +16.5%, $p = 0.055$). In running with the individually moulded insole with medial arch support, the percentage of the total force-time integrals before and after the run significantly increased from 8.5% to 10.6% (% change = +24.7%, $p = 0.004$). There is also a generally significant reduction among the metatarsal regions (M05-M07) for both insoles after the run (from -7.0% to -17.5%). This indicated the medial mid-foot shared more of the loading from the metatarsal regions. This is probably because of the introduction of the medial arch support conforming to the foot contour, thereby providing a more even contact over the entire plantar surface to spread out the load.

Significance

This study showed that after a one-hour treadmill run at 10 km/h, peak pressure and peak force increased at the heel for both flat and arch supported insoles, but the medial arch supported insole significantly reduced these values when compared to the flat insole. Loading, as shown by the percentage of the total force-time integrals, was increased in the medial mid-foot when the participants ran with the individually moulded insole with medial arch support. We concluded that an individually moulded insole with medial arch support is effective in reducing impact and loading under the heel during prolonged running on a treadmill, probably by shifting the load to the medial mid-foot supported by the insole with medial arch support. We hope that the results can aid runners to choose suitable functional shoes or insoles for preventing injuries caused by repetitive impact to the heel.

Conflict of interest statement

All authors declared no potential conflict of interest.

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Figure legends

Fig 1 – The two insoles used in this study: (1) flat insole; (2) insole with medial arch support.

Fig 2 – The ten anatomical regions in the insole used in this study: medial heel (M01), lateral heel (M02), medial mid-foot (M03), lateral mid-foot (M04), 1st metatarsal head (M05), 2nd and 3rd metatarsal heads (M06), lateral metatarsal heads (M07), hallux (M08), 2nd and 3rd toes (M09) and lateral toes (M10).

Figure 1

(1) Flat insole

(2) Insole with medial arch support

Figure2

Table 1

Table 1. The peak pressure, peak force, time normalised pressure time integrals, and percentage of the total force-time integrals of the ten plantar regions with the two insoles at initial run and final run

Region	<u>Initial Run (IR)</u>		<u>Final Run (FR)</u>		<u>Percentage change and p-value from paired t-test in brackets</u>			
	Flat insole (F)	Medial arch supported insole (A)	Flat insole (F)	Medial arch supported insole (A)	F-A (at Initial Run)	F-A (at Final Run)	IR-FR (for Flat insole)	IR-FR (for Medial arch supported insole)
Peak pressure (kPa)								
M01	211.3 (34.9)	197.3 (28.1)	250.0 (31.5)	216.8 (28.6)	-6.6% (0.074)	-13.3% (0.005*)	+18.3% (0.001*)	+9.9% (0.016*)
M02	216.7 (35.3)	205.2 (30.1)	255.8 (33.6)	230.5 (20.5)	-5.3% (0.170)	-9.9% (0.006*)	+18.0% (0.006*)	+12.3% (0.002*)
M03	162.7 (31.3)	152.3 (28.6)	190.8 (34.8)	167.6 (28.8)	-6.4% (0.317)	-12.1% (0.007*)	+17.3% (0.003*)	+10.0% (0.003*)
M04	149.6 (24.1)	152.0 (33.1)	170.2 (30.3)	163.1 (30.0)	+1.6% (0.797)	-4.1% (0.695)	+13.8% (0.007*)	+7.3% (0.007*)
M05	261.5 (60.7)	258.2 (47.9)	256.7 (53.9)	264.8 (56.4)	-1.2% (0.888)	+3.2% (0.261)	-1.8% (0.683)	+2.6% (0.559)
M06	231.5 (46.3)	244.3 (33.1)	246.9 (46.1)	258.3 (38.5)	+5.5% (0.164)	+4.6% (0.132)	+6.7% (0.100)	+5.7% (0.024*)
M07	197.5 (30.9)	208.4 (37.6)	203.1 (31.2)	207.3 (35.2)	+5.5% (0.149)	+2.1% (0.620)	+2.8% (0.131)	-0.5% (0.861)
M08	286.5 (64.5)	287.0 (39.7)	266.7 (60.7)	266.7 (37.2)	+0.2% (0.810)	+0.0% (0.902)	-6.9% (0.193)	-7.1% (0.132)
M09	183.1 (51.8)	203.0 (38.7)	197.1 (61.3)	218.2 (40.9)	+10.9% (0.108)	+10.7% (0.127)	+7.6% (0.276)	+7.5% (0.026*)
M10	116.9 (51.9)	125.7 (57.3)	127.9 (51.6)	127.3 (44.9)	+7.5% (0.240)	-0.05% (0.513)	+9.4% (0.185)	+1.3% (0.869)
Peak force (N)								
M01	194.6 (36.3)	164.9 (36.9)	228.6 (43.4)	187.9 (36.6)	-15.3% (0.001*)	-17.8% (0.006*)	+17.5% (0.005*)	+13.9% (0.033*)
M02	360.3 (62.3)	291.2 (117.3)	383.0 (86.4)	342.0 (71.8)	-19.2% (0.037*)	-10.7% (0.345)	+6.3% (0.438)	+17.4% (0.083)
M03	201.5 (67.0)	207.6 (39.7)	225.8 (53.6)	220.7 (42.4)	+3.0% (0.951)	-2.3% (0.382)	+12.1% (0.013*)	+6.3% (0.078)
M04	297.5 (28.7)	285.8 (41.6)	324.0 (38.2)	307.5 (49.9)	-3.9% (0.299)	-5.1% (0.205)	+8.9% (0.011*)	+7.6% (0.041*)
M05	243.4 (47.7)	227.4 (46.3)	232.6 (50.5)	233.6 (55.6)	-6.6% (0.339)	+0.4% (0.939)	-4.4% (0.359)	+2.7% (0.369)
M06	306.4 (42.9)	301.8 (40.7)	304.2 (35.5)	314.9 (45.7)	-1.5% (0.918)	+3.5% (0.282)	-0.7% (0.805)	+4.3% (0.059)
M07	196.1 (33.0)	208.3 (46.8)	200.2 (40.0)	215.1 (50.9)	+6.2% (0.198)	+7.4% (0.171)	+2.1% (0.535)	+3.3% (0.442)
M08	171.7 (37.7)	173.4 (31.4)	170.4 (35.5)	165.6 (25.6)	+1.0% (0.822)	-2.8% (0.482)	-0.8% (0.831)	-4.5% (0.386)
M09	101.3 (28.6)	104.7 (31.7)	119.2 (36.5)	105.7 (38.3)	+3.4% (0.503)	-11.3% (0.283)	+17.7% (0.062)	+1.0% (0.865)
M10	38.0 (15.5)	41.5 (21.3)	46.2 (17.9)	42.7 (18.6)	+9.2% (0.296)	-7.6% (0.677)	+21.6% (0.031*)	+2.9% (0.496)

Time normalised pressure-time integrals (kPa)								
M01	206.2 (74.4)	227.2 (134.4)	402.0 (139.9)	365.2 (87.9)	+10.2% (0.742)	-9.2% (0.402)	+95.0% (<0.001*)	+60.7% (0.001*)
M02	216.0 (96.2)	255.2 (134.2)	421.5 (159.3)	503.3 (213.7)	+18.1% (0.506)	+19.4% (0.086)	+95.1% (0.001*)	+97.2% (0.004*)
M03	206.1 (60.3)	204.0 (83.7)	334.6 (89.2)	323.3 (60.6)	-1.0% (0.858)	-3.4% (0.519)	+62.3% (<0.001*)	+58.4% (<0.001*)
M04	226.1 (45.4)	220.4 (69.6)	339.7 (79.7)	320.9 (62.9)	-2.5% (0.788)	-5.6% (0.419)	+50.2% (0.001*)	+45.6% (0.005*)
M05	395.1 (116.2)	382.2 (116.3)	524.9 (147.4)	533.5 (120.1)	-3.3% (0.753)	+1.6% (0.671)	+32.9% (0.010*)	+39.6% (<0.001*)
M06	374.5 (97.6)	384.2 (107.9)	513.2 (123.0)	532.8 (78.7)	+2.6% (0.837)	+3.8% (0.532)	+37.0% (0.006*)	+38.7% (<0.001*)
M07	324.4 (74.6)	324.4 (90.7)	443.9 (84.8)	455.4 (90.4)	+0.0% (0.999)	+2.6% (0.598)	+36.8% (0.005*)	+40.4% (0.001*)
M08	433.6 (131.8)	407.5 (96.5)	554.5 (151.9)	519.8 (83.2)	-6.0% (0.530)	-6.3% (0.401)	+27.9% (0.008*)	+27.6% (0.013*)
M09	283.4 (99.9)	312.6 (93.7)	444.2 (161.2)	463.4 (85.7)	+10.3% (0.368)	+4.3% (0.559)	+56.7% (0.002*)	+48.2% (<0.001*)
M10	181.8 (88.0)	188.5 (94.5)	315.1 (123.0)	298.1 (82.0)	+3.7% (0.611)	-5.4% (0.920)	+73.3% (0.001*)	+58.1% (0.002*)
Percentage of the total force-time integrals (%)								
M01	6.2 (1.8)	5.8 (2.2)	8.4 (1.8)	6.4 (1.2)	-6.5% (0.343)	-23.8% (0.004*)	+35.5% (<0.001*)	+10.3% (0.221)
M02	10.6 (3.5)	10.4 (3.0)	13.2 (2.3)	11.4 (1.9)	-1.9% (0.241)	-13.6% (0.022*)	+24.5% (0.029)	+9.6% (0.283)
M03	7.8 (2.9)	8.5 (2.1)	9.1 (1.7)	10.6 (2.4)	+9.0% (0.210)	+16.5% (0.055)	+16.7% (0.118)	+24.7% (0.004*)
M04	13.8 (2.2)	13.3 (1.3)	13.6 (2.3)	13.5 (2.7)	-3.6% (0.478)	-0.7% (0.532)	-1.4% (0.787)	+1.5% (0.690)
M05	13.7 (2.5)	13.1 (2.8)	11.3 (2.3)	11.9 (2.4)	-4.4% (0.672)	+5.3% (0.543)	-17.5% (0.002*)	-9.2% (0.019*)
M06	18.5 (2.3)	18.5 (2.5)	15.4 (2.2)	17.2 (2.2)	+0.0% (0.798)	+11.7% (0.013*)	-16.8% (0.004*)	-7.0% (0.013*)
M07	11.6 (2.1)	11.9 (2.1)	10.4 (2.3)	11.6 (2.3)	+2.6% (0.560)	+11.5% (0.080)	-10.3% (0.032*)	-2.5% (0.545)
M08	9.8 (2.6)	9.9 (2.4)	8.8 (2.0)	8.4 (2.3)	+1.0% (0.630)	-4.5% (0.849)	-10.2% (0.106)	-15.2% (0.032*)
M09	6.0 (1.6)	6.2 (2.1)	7.1 (2.0)	6.3 (2.7)	+3.3% (0.469)	-11.3% (0.472)	+18.3% (0.041*)	+1.6% (0.928)
M10	2.1 (0.8)	2.3 (1.1)	2.7 (0.9)	2.7 (1.1)	+9.5% (0.309)	+0.0% (0.863)	+28.6% (0.006*)	+17.4% (0.096)

* indicates significant difference (p < 0.05)

Conflict of interest statement

All authors declared no potential conflict of interest.