

# FACTORS ASSOCIATED WITH NIGHT-TIME CALF MUSCLE CRAMPS: A CASE-CONTROL STUDY

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**ABSTRACT:** *Introduction:* Although highly prevalent and painful, night-time calf muscle cramping is poorly understood, and no treatment has shown consistent efficacy or safety. *Methods:* One hundred sixty adults were recruited from New South Wales, Australia, including 80 who had night-time calf cramping at least once per week and 80 age- and gender-matched adults who did not. Participants were assessed using reliable tests of lower limb strength, flexibility, morphometrics, circulation, and sensation, and were questioned about health and lifestyle factors, diet, medications, exercise, symptomatology, sleeping habits, and footwear. *Results:* Conditional logistic regression identified 3 factors independently associated with night-time calf muscle cramps: muscle twitching (OR 4.6, 95% CI 1.6–15.5,  $P = 0.01$ ); lower limb tingling (OR 4.1, 95% CI 1.6–10.3,  $P = 0.003$ ); and foot dorsiflexion weakness (OR 1.02, 95% CI 1.01–1.03,  $P = 0.002$ ), which represented other measures of lower limb weakness in the model. *Conclusions:* Night-time calf muscle cramps were associated with markers of neurological dysfunction and potential musculoskeletal therapeutic targets.

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Approximately one third of all adults<sup>1</sup> and one half of adults >60 years of age<sup>2</sup> have night-time cramping of the calf muscles (gastrocnemius–soleus complex). The impact of night-time calf muscle cramps on the individual is broad and can be debilitating. The literature abounds with reports of cramp-induced distress,<sup>3,4</sup> disability,<sup>5,6</sup> reduced sleep quality,<sup>1,7,8</sup> reduced quality of life,<sup>7,9</sup> and interference with activities of daily living.<sup>10</sup> Furthermore, in a study of 51 nursing home residents without dementia, leg cramping, as part of a group of sleep disturbances, was independently associated with depressive symptoms.<sup>11</sup>

Muscle cramps exhibit high rates of repetitive firing of motor unit action potentials<sup>7</sup> and involve fewer muscle fibers than voluntary contraction.<sup>12</sup> Each cramp exhibits 1 or more foci of motor unit action potential activity that shifts location during the cramp, but never jumps from 1 region to another.<sup>13</sup> The acute pain of muscle cramps ranges from mild to excruciating.<sup>14,15</sup> Muscle cramping can first occur at any age, but it is unlikely to

occur in childhood without the presence of neurological disease.<sup>7,16</sup> Although the neuronal mechanism of cramping is not fully understood, 2 enduring hypotheses suggest involvement of abnormal excitability of motor nerve terminals and instability of groups of anterior horn cells due to spinal disinhibition.<sup>12,17</sup>

The cause of cramping is poorly understood, and there is global controversy regarding drug therapy. Quinine is widely prescribed in the UK for muscle cramps, but it is currently banned in the USA and Australia as a treatment for muscle cramps due to concerns regarding adverse effects, particularly thrombocytopenia.<sup>4,18</sup> No non-drug therapy has been adequately evaluated in clinical trials.<sup>19</sup> The aim of this study was to identify factors associated with night-time calf cramping in adults to reveal etiological correlates and modifiable treatment targets.

## METHODS

Between August 2010 and October 2011, 80 adults who experience night-time calf muscle cramping at least once per week and 80 adults without night-time calf muscle cramping volunteered to attend a single study visit that included a thorough clinical assessment and completion of a self-report survey. Non-cramping controls were age ( $\pm 3$  years) and gender matched to the cramping cases. Muscle cramp was defined as “a sudden, involuntary and painful contraction of muscle that gradually lessens. During cramp, the affected muscle hardens, and joints can be forced into unusual positions. In some people, cramp can be brought on by certain movements and/or stopped by stretching the muscle.” This definition was based on descriptions reported in the literature<sup>1,2,15</sup> and clinical experience in describing cramping to patients. Exclusion criteria included dementia, lower limb injury that prevented participation in clinical testing, and conditions known to cause cramps, including neuromuscular or neurological disease (e.g., Charcot-Marie-Tooth disease, amyotrophic lateral sclerosis, Guillain-Barré syndrome), nerve root compression, pregnancy, and hemodialysis. All study subjects were proficient in English, ambulant, and agreed

**Abbreviation:** FPI, foot posture index

**Key words:** calf muscle, hamstring, muscle cramp, sleep disturbance, treatment

Additional Supporting Information may be found in the online version of this article.

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to participate in accordance with the guidelines of the human research ethics committee of the University of Newcastle (H-2010-1041).

Participants were recruited from the Newcastle, Central Coast, and Hunter Valley regions of New South Wales, Australia. Recruitment for the study was promoted on regional television news and radio, in 4 regional newspapers, in reception areas of a podiatry practice, at the university clinic and local general practice, and by contacting local community groups (e.g., Lions and Rotary Clubs). Data collection sites were off-campus teaching clinics of the University of Newcastle and 2 local private medical/podiatry clinics.

**Physical Measures.** The principle investigator (F.H.) conducted a preliminary study demonstrating excellent test-retest reliability (intraclass correlation coefficient  $>0.75$  for continuous data,<sup>20</sup> kappa = 1.0 for dichotomous data) of all included clinical tests on 10 potential participants prior to commencing the study (see supplementary material, Tables S1 and S2). The order of physical measures was consistent among participants. A complete description of physical measures is available online as supplementary material. Strength was measured according to hand-held dynamometry for foot eversion, inversion, plantarflexion, and dorsiflexion strength<sup>21</sup>; ability to walk 6 steps on “tip-toe”<sup>22</sup>; and the “paper grip test” for toe strength.<sup>23</sup> Flexibility was measured using the lunge test (weight-bearing ankle dorsiflexion range),<sup>24</sup> non-weight-bearing ankle dorsiflexion range, and knee extension angle (hamstring flexibility).<sup>25</sup> Sensation was measured using Semmes-Weinstein grade 5.07 (10-g) monofilament (North Coast Medical, Aracata, California) plantar to the distal hallux, third metatarsophalangeal joint, and fifth metatarsophalangeal joint,<sup>26,27</sup> and a new Rydel-Seiffer C 64-Hz/c128-Hz graded tuning fork (Granton Medical, Sheffield, UK)<sup>28</sup> at the dorso-medial aspect of the first metatarsophalangeal joint. As an indicator of fasciculation, participants were asked whether they had muscle twitching. Anthropometric measures included height, weight, maximum calf circumference,<sup>29</sup> and foot posture index.<sup>30</sup> Blood flow was measured by hallux blood pressure<sup>31</sup> and history of intermittent claudication.<sup>32</sup>

**Survey.** The custom-designed survey was pilot-tested for content validity by 4 podiatrists with experience in treating night-time muscle cramps, by 2 non-health professionals who had night-time calf cramping, and by 2 non-health professionals who did not have night-time calf cramping. The survey comprised questions covering factors identified in the literature as potentially contributing to cramping and those factors plausibly associated. Self-

reported items related to: smoking history; alcohol consumption<sup>33</sup>; adherence to Australian national dietary guidelines for adults<sup>34</sup>; fluid consumption<sup>34</sup>; hours of physical exercise per week; sleeping position; sensation of cold feet while in bed at night; usual timing of bath or shower; presence of varicose veins; use of medical compression stockings; presence of tingling of feet and/or legs; use of high-heel shoes; regular stretching of calf muscle; markers of general health (including the number of different prescribed medications taken per day, the number of tablets taken per day, and the number of surgeries that required general anesthesia); and diagnosis of current lower back pain, sciatica, osteoarthritis of hip or knee, rheumatoid arthritis, anxiety disorder, migraine, alcohol or drug-use disorder, kidney problems, depression, or diabetes (see supplementary material for survey).

**Statistical Analyses.** For participants who had cramping unilaterally ( $n = 8$ ), only data from the affected leg were included in analyses. For all other participants, a random limb was selected using a computer-generated random number list. Data were transcribed to SPSS, version 19.0 (Chicago, Illinois), and checked for transcription errors. Continuous data were tested for normality using the Kolmogorov-Smirnov test and by inspecting histograms. The appropriate parametric or non-parametric test was subsequently employed. The relationships between participant characteristics, physical measures, and survey data with presence of night-time calf muscle cramping were explored with a point-biserial correlation coefficient for normally distributed continuous data, the Spearman rho for non-normally distributed continuous data, chi-square test for categorical data when  $\leq 20\%$  of cells had an expected cell count  $<5$  (with Yates continuity correction for  $2 \times 2$  tables), and the Fisher exact test for categorical data when  $>20\%$  of cells had an expected cell count  $<5$ . Missing data were addressed by excluding cases pairwise.

Physiologically plausible factors significantly ( $P < 0.05$ ) associated with presence of night-time calf muscle cramps were entered into a conditional logistic regression model, adjusting for the matching variables of age and gender. To avoid multicollinearity, only 1 variable from highly correlated ( $r > 0.7$ ) variables (e.g., foot eversion, inversion, plantarflexion, and dorsiflexion strength) was included. Removal testing used the stepwise, backward elimination method based on the Wald statistic. The omnibus tests of model coefficients were performed to provide an overall indication of the model's performance.<sup>35</sup> An odds ratio and 95%

**Table 1.** Characteristics of cramping for cases and controls.

Characteristic	Cases	Controls
Gender [n (%)]		
Female	47 (59%)	47 (59%)
Male	33 (41%)	33 (41%)
Age (years)	71 (10)	71 (10)
Height (cm)	167 (9)	166 (11)
Mass (kg)	79 (16)	78 (18)
BMI (kg/m <sup>2</sup> )	28.2 (5.1)	28.3 (5.3)
Socioeconomic index score*	970 (32)	982 (42)

Data expressed as mean (SD), unless otherwise noted.  
 \*Calculated using the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA), Postal Areas.<sup>60</sup>

confidence interval (CI) were calculated for each independent variable in the model.

**RESULTS**

Of 164 potential participants screened, 160 adults (age range 34–95 years) met the inclusion criteria and volunteered to participate. Of the 4 individuals who did not participate, 1 “decided against it,” 1 could not find the time, 1 requested payment, and 1 did not respond to follow-up phone calls and e-mails. Table 1 compares participant characteristics between groups. Factors statistically significantly associated with night-time calf cramps were weakness of foot inversion, eversion, dorsiflexion and plantarflexion, weakness of hallux and lesser digit grip, greater difficulty in walking on tip-toe, hamstring tightness, presence of muscle twitching, presence of tingling in feet or legs, sensation of cold feet at night while in bed, greater self-reported fluid consumption, presence of calf pain that is not muscle cramp (nor intermittent claudication), and decreased prevalence of self-reported migraines. Among cases, the most common timing of muscle twitching was at rest (*n* = 11), after physical activity (*n* = 7), and before muscle cramping (*n* = 5). The relationships between night-time calf cramps and all measured participant characteristics are indicated in the online supplementary material (Tables S3 and S4).

**Logistic Regression.** The variables entered into the stepwise logistic regression model were muscle twitching, lower limb tingling, foot or leg coldness while in bed at night, foot dorsiflexion strength, hamstring flexibility, and hallux and lesser digit grip strength. Logistic regression identified presence of muscle twitching, lower limb tingling, and dorsiflexion weakness as independent correlates of night-time calf muscle cramping. Table 2 summarizes the conditional logistic regression model. When controlling for the influence of other predictor variables, the odds of calf muscle cramping are 4.6 (95% CI 1.6–15.5) times higher for an adult with muscle twitching, 4.1 (95% CI 1.6–10.3)

times higher for an adult with lower limb tingling, and 1.02 (95% CI 1.01–1.03) times higher for each newton of foot dorsiflexion weakness.

**DISCUSSION**

Increased prevalence of muscle twitching and lower limb tingling in those with night-time calf muscle cramping was independent of the presence of diabetes or sensory deficit detected with grade 5.07 monofilament or 64-Hz tuning fork. The association between muscle twitching (fasciculation) and muscle cramping has long been recognized.<sup>5,36–38</sup> The association between calf cramps and lower limb tingling (or any other form of paresthesias) is less well documented. We are aware of only 1 other study that has reported on paresthesias among individuals with muscle cramp. Yunus, in 1996, reported a correlation between “leg cramps” and “paresthesia” in 135 women with fibromyalgia. No data were provided on the type or site of cramping or the site of paresthesia.<sup>39</sup> There is mounting evidence in the literature to support that muscle cramping is due to dysfunction (namely, hyperexcitability) of motor nerves.<sup>40–44</sup> Our findings suggest that hyperexcitability might occur concurrently in sensory nerves in the form of tingling.

All measures of foot, ankle, and toe strength were lower in subjects with night-time calf cramping. This weakness was detected despite no difference in reported hours of exercise participation per week. As weakness was identified in muscles that did and did not cramp, weakness is not a result of recurrent episodes of cramp-induced muscle damage. It is not entirely clear from this cross-sectional study whether weakness predisposes to cramp or whether cramps and muscle weakness share a similar cause (e.g., neurological dysfunction).<sup>7</sup> Muscle weakness is a normal age-related neuromuscular change<sup>45</sup> and is not completely

**Table 2.** Logistic regression analysis on factors associated with night-time calf cramping.

Variable	β	SE β	Wald's $\chi^2$	df	P	Odds ratio
Muscle twitching	1.5	0.6	6.1	1	0.01	4.6 (1.6–15.5)
Lower limb tingling	1.4	0.5	8.8	1	0.003	4.1 (1.6–10.3)
Dorsiflexion strength	-0.02	0.006	9.3	1	0.002	1.02 (1.01–1.03)
			$\chi^2$			
Omnibus test			40.4	3	<0.001	

\*Odds ratios for the continuous variables show the increase in odds per unit of measure (e.g., for each additional degree of dorsiflexion weakness).

explained by reduced physical activity.<sup>46</sup> Other age-related neuromuscular changes include reduced size of type II (fast twitch) muscle fibers,<sup>47</sup> reduced contribution of type II muscle fibers to force generation,<sup>48</sup> decreased total motor unit number,<sup>49</sup> and increased size (or innervation ratio) of each motor neuron.<sup>50</sup> Further research is required to determine whether adults who have night-time muscle cramping demonstrate greater age-related neurophysiological and electromyographic changes than age-matched controls. Of note, Teleman and colleagues reported an unusual predominance of type II muscle fibers in 5 adults, aged 28–48 years, who had unspecified cramps.<sup>51</sup> Again, further research will be needed to determine whether this is true in older adults with night-time calf muscle cramping. As age-related changes affect type II fibers more than type I fibers, those individuals with a predominance of type II muscle fibers may be exposed to a greater impact of age-related changes. Muscle strength training in older adults promotes neurological adaptation and muscle hypertrophy<sup>52</sup> and could be explored as a potential therapeutic target for night-time calf cramps.

Hamstring tightness and foot or leg coldness while in bed at night were associated with night-time calf cramps but were not independent correlates. As these factors are potentially more readily modifiable than the identified independent correlates, they may be worthwhile therapeutic targets. The difference in mean hamstring flexibility between groups was 8° (13%). Tightness of the hamstring but not of the calf suggests that the tightening is not due to the muscle cramp. Hamstring flexibility was measured with the thigh held in a vertical position and the knee gradually extended with the foot in a relaxed position to reduce risk of neural tension.<sup>25,53</sup> Hamstring tightness may cause the knee to rest in a more flexed position during sleep. The flexed knee position is used in clinical research protocols to induce cramping,<sup>13</sup> but it has not been reported as a potential cause of night-time calf cramps. It is not clear whether night-time foot or leg coldness reported by participants is a physical coldness or a sensation of coldness due to neurological dysfunction. If the coldness is physical, then this coldness may prompt a person to move the legs during the night, which could trigger cramping. An observational study of sleep position prior to cramping may test these hypotheses. Nevertheless, hamstring stretching (for which there are effective techniques to increase range<sup>54</sup>) and temperature control could form the basis of a non-drug therapy clinical trial for prevention of recurrent night-time calf cramping.

There were a number of surprising findings from this study. Previous research has investigated

calf muscle stretching to prevent night-time calf cramping. Although stretching the calf muscle is an accepted treatment for terminating acute cramps,<sup>3,10,55–57</sup> calf stretching as a preventative intervention lacks indication and evidence of effectiveness. Fluid consumption was associated with calf cramps but was not entered into the logistic regression model. Participants who had night-time calf cramps were more likely to report drinking at least 1.5 L of fluid each day, but 45% of cramping cases reported drinking more water to try to prevent night-time muscle cramp, which likely explains the association. Those who did not have night-time calf cramps were more likely to report migraines. This was not entered into the logistic regression model, as it lacked physiological plausibility. Those with night-time calf cramping were more likely to report having cold feet at night. It cannot be determined from these data whether the foot coldness was due to reduced blood flow or whether there was a sensation of coldness due to neurological dysfunction. Cold feet at night was not an independent predictor of cramping, suggesting that the relationship must be explained by other variables in the model (e.g., lower leg tingling). Our study found no association between night-time calf cramps and peripheral blood flow (measured using hallux blood pressure and experience of intermittent claudication). This supports the neurological hypothesis for origin of cramping. Night-time calf cramping was also not associated with smoking history or alcohol consumption. Our survey did not include questions about caffeine consumption or the type of medications participants were using. Many medications have been reported to increase risk of cramps,<sup>58,59</sup> yet insufficient data were available at the time of planning this study on the dose and duration of medication, and type and location of cramping.

Results of this study should be interpreted in light of some potential limitations. Despite an age- and gender-matched control group, the cross-sectional nature of this study limits inferences about any cause–effect relationships. Fluid consumption, diet quality, and physical activity data relied on participant recall and self-report. Use of a food diary and a validated questionnaire for habitual physical activity (e.g., International Physical Activity Questionnaire) would provide more accurate measures. Results of this study should not be generalized to patients diagnosed with a neurological condition known to cause cramps or to other forms of cramps, such as those associated with exercise, pregnancy, or hemodialysis.

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