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EXERCISE-ASSOCIATED MUSCLE CRAMP

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- Exercise-associated muscle cramp (EAMC) is a temporary, but intense and painful, involuntary contraction of skeletal muscle occurring during or soon after a period of physical activity.
- EAMC is highly unpredictable, and some individuals appear more susceptible than others.
- Single small muscles (often those in the hand or foot) or multiple large muscle groups may be involved.
- Proposed mechanisms include disturbances of water and electrolyte balance and abnormal spinal reflex activity.
- It seems likely that different mechanisms may operate in different scenarios.
- No prevention strategy or treatment is consistently effective: trial and error may help to establish effective procedures.

INTRODUCTION

Cramp is the term used to describe an intense, involuntary, and often painful contraction of skeletal muscle. Cramps occur in many different situations. They commonly affect large muscle groups when prolonged work is carried out, especially in hot environments, but also occur in small muscle groups exposed to repetitive contractions, as in typists or writers. Cramps may also occur in the absence of exercise, as in pregnancy or renal dialysis as a side effect of some medications (Maughan and Shirreffs, 2019). Whatever form they take, they are notoriously unpredictable, making them hard to study and suggesting, perhaps, that different causal factors may be involved.

Exercise-associated muscle cramp (EAMC) has been defined as a "painful, spasmodic contraction of the skeletal muscle that occurs during or immediately after muscular exercise" (Schwellnus et al., 1997). The pain and disability that results are usually sufficient to prevent, or at least severely limit, movement of the affected limbs, though the condition normally resolves without intervention. Resolution may take from a few seconds to a few minutes, but the afflicted limb is not functional during this time and perhaps for some time afterward.

The prevalence of EAMC has been assessed in different sport populations, but different definitions and different assessment tools have been applied over variable time periods, confounding comparisons between studies. Schwabe et al. (2014) reported the incidence of serious muscle cramping to be less than one per thousand runners in a large cohort (65,865 runners) of participants in half marathon and ultramarathon events, but others have reported much higher rates. Maughan (1986) found that 15 out of a sample of 82 (18%) male marathon runners, of varying performance level, reported cramp during a single race. To put these data in perspective, Abdulla et al. (1999) reported that in an older, non-exercising patient group aged 65 years or older, 50% experienced frequent muscle cramps. Most of these cases of muscle cramps in the general population are not associated with exercise but with a range of clinical conditions or the use of drugs for the treatment of those conditions (Maughan & Shirreffs, 2019).

Much has been made of the need to understand the causes of muscle cramps and of the underlying physiological processes. However, the primary concern should be to identify effective preventive strategies and treatments, and it must be recognized that an understanding of mechanisms (interesting as it is) is not necessary to develop treatment strategies. Potential causes of cramp have been investigated in numerous epidemiological studies involving large numbers of participants in mass-participation endurance events. While such studies may reveal associations, they cannot establish causation and do not lend themselves to assessment of the efficacy of different interventions. Experimental models that can more reliably induce cramping in the laboratory can be used to design randomized placebo-controlled intervention trials. These models, however, may not reflect the spontaneous cramps that occur in athletes in training or competition.

RESEARCH REVIEW

Any attempt to study the causes and treatment of EAMC is inevitably frustrated by its unpredictability. Exercise in the laboratory seldom results in cramp, even among those who report frequent cramping during training. Field studies, where individuals in mass-participation events who suffer from cramps are compared with a cramp-free control group, suffer from a lack of standardization of conditions, making true comparisons difficult to achieve. These difficulties have led to the study of different models, which may account for the different conclusions that have been reached about the underlying causes of EAMC. These models include:

- Spontaneous cramps occurring in industrial settings involving large populations at risk. Such groups have included physically demanding occupations, such as mining and construction work, as well as less demanding repetitive tasks using small muscle groups, such as writing, typing or telegraphy.
- Spontaneous cramps occurring during training or competitive sporting events.

- Laboratory models where cramps are induced by voluntary or electrically evoked activation of small muscle groups held in a shortened position.

The older literature contains many detailed reports on the incidence of EAMC and potential preventive strategies from a range of occupational settings. The more recent literature has focused on cross-sectional studies of participants in mass-participation endurance events and on laboratory models.

This uncertainty is reflected in the conclusion of recent reviews that the causes of EAMC, and therefore the treatment options, continue to be uncertain (Jahic & Begic, 2018; Swash et al., 2019). Two main hypotheses have been proposed and continue to be debated: a disturbance of water and salt balance and a neurological cause resulting in sustained abnormal discharge of motor drive to the afflicted muscles (Giuriato et al., 2018). Each of these hypotheses has strong advocates and has some support but neither can fully explain the nature of EAMC.

Disturbances of Water and Salt Balance

The strongest evidence that sweat-related electrolyte imbalances are a factor in some muscle cramps is found in the large-scale observational and prospective studies of industrial workers — mainly studies on miners, ship's stokers, construction workers and steel mill workers that were conducted in the 1920s and 1930s — where administration of saline drinks or salt tablets was able to greatly reduce the incidence of cramps (Moss, 1923; Talbott, 1935; McCord & Ferenbaugh, 1931; Talbott & Michelsen, 1933; Dill et al., 1936). These studies were inevitably limited by the methods available at the time, but they did have the advantage of access to large populations and the keeping of careful medical records related to productivity. It is easy to dismiss much of the older literature, but some of the observations were extensive and meticulous.

Though methodologies were limited, many of the observations were remarkably prescient. For example, Moss (1923) published an extensive report in which he documented cases of cramp among coal miners and the factors that may have contributed to the development of these cramps. He attributed the onset of cramps, which in some cases were seriously debilitating, to:

1) High air temperatures
2) Excessive drinking of water caused by dryness of the mouth and throat
3) Continued hard work

He also observed that cramps tended to occur during the second half of a working shift and in men who were less physically fit, thus implicating not only sweat losses, but also fatigue in the etiology. It should be noted that cramp was not attributed to dehydration or to increased serum electrolyte concentrations, but rather "to a form of water poisoning of the muscles brought about by the combination of great loss of chloride by sweating, excessive drinking of water, and temporary paralysis of renal excretion" (Anon, 1923). Chloride was normally measured in body fluids as there was no good assay for sodium at the time, but there is a close relationship between sodium and chloride concentration in sweat (Shirreffs & Maughan, 1997). These observations do not implicate dehydration, as most later writers say, but rather inappropriate, and perhaps excessive, intake of plain water in combination with large losses of electrolytes in sweat.

It is also not correct to say that there have been no large-scale prospective studies to assess the role of water and salt balance in the etiology of muscle cramps. Dill et al. (1936) reported the findings of intervention studies carried out at the construction site of the Hoover Dam and in the steel mills of Youngstown, Ohio. At both locations, large numbers of men undertook hard physical work in extremely hot environments on a daily basis. They found that those suffering from cramp displayed the following characteristics:

1) Dehydration
2) Lowered concentration of sodium and chloride in blood plasma
3) Little or no sodium or chloride in urine
4) Increased serum protein concentration
5) Increased red cell count
6) Normal osmotic pressure

This presents a complex picture: some of these findings are typical of dehydration (1, 4 and 5), while others are consistent with overhydration (2, 3). They also reported, however, that injection of isotonic saline normalized the blood profile and brought immediate relief from the symptoms. In the largest intervention study, reported in the same paper, they added saline to the water given to the 12,000 men employed in one of the mills while those at neighboring mills continued to be provided with plain water. This was effective in almost completely abolishing cases of muscle cramp, though in previous years and at other mills in the same year where plain water was given, up to 12 cases of cramp required hospitalization in a single day.

Severe restriction of dietary sodium intake can also result in hyponatremia and may be associated with generalized skeletal muscle cramping in the absence of exercise (McCance, 1936). This may be relevant today in light of the common advice that dietary salt intake should be reduced to minimize risks of hypertension (Ha, 2014). Several studies have assessed changes in hydration status and plasma electrolyte concentrations in athletes who have experienced muscle cramps, and these studies have included marathon runners, participants in a 56 km road race, competitors in an Ironman triathlon, and participants in a 161 km ultramarathon (see Maughan, 1986; Maughan & Shirreffs, 2019, for details of these studies). None of these showed any association between cramp and serum electrolyte changes, but it is important to note that serum electrolyte concentrations may be of little relevance. Local intracellular and extracellular electrolyte concentrations may be relevant, as they will affect the resting membrane potential of both muscles and nerves, but it is unlikely that changes in plasma concentrations can track these changes. There is good evidence that changes in the plasma concentration of these electrolytes may not reflect local intramuscular changes during either intense or prolonged exercise (Sjøgaard, 1986; Costill et al., 1976). It is also the case that blood samples have usually not been collected at the time of cramping,

but only later, once the cramping had resolved, and in some cases this was several hours after resolution of the cramps, so the absence of any association is perhaps not surprising.

Stofan et al. (2005) found that sweat sodium losses during training sessions were larger in a group of cramp-prone football players (n = 5) than in players with no history of EAMC. The same research group later investigated a group of American football players without a cramping history (n = 8) and a cramp-prone group (n = 6) (Horswill et al., 2009). Whole blood sodium concentration (as stated by the authors, but in reality this is plasma sodium concentration) remained unchanged after training in the control group (138.9 ± 1.8 to 139.0 ± 2.0 mmol/L), while it tended to decline (137.8 ± 2.3 to 135.7 ± 4.9 mmol/L) in the cramp-prone players, and three subjects in this group recorded values below 135 mmol/L. Those in the cramp-prone group consumed a greater percentage of their total fluid as plain water rather than electrolyte-containing sports drinks (though the difference in sodium intake was small) and had a higher sweat sodium concentration (53 ± 29 vs. 38 ± 18 mmol/L), and thus incurred a greater sodium deficit over the course of the training session.

A laboratory study by Ohno and Nosaka (2004) showed that a body fluid deficit of 3% body mass induced by intermittent sauna exposure without exercise increased the number of subjects who developed cramps during a muscle cramp test in the toe flexors but not in the knee extensors. Jung et al. (2005) had participants perform a fatiguing protocol in the calf muscles to induce EAMCs. In one trial, subjects consumed a carbohydrate-electrolyte drink at a rate similar to sweat rate and in the other trial, no fluid was consumed and mild (1% loss of body mass) hypohydration developed. Nine participants experienced cramps in the carbohydrate-electrolyte trial, compared with seven in the hypohydration trial. Of the seven individuals who had EAMC in both trials, time to onset was more than doubled in the carbohydrate-electrolyte trial (36.8 ± 17.3 min) compared with the hypohydration trial (14.6 ± 5.0 min). Subjects who experienced cramps sweated more (2.0 ± 0.9 L/min) than those who did not (1.3 ± 0.6 L/min). It is not clear whether there was any treatment order effect in these studies that might have confounded the results: this is discussed further below.

More recently, Ohno et al. (2018) systematically investigated the susceptibility of voluntarily induced cramp in hamstrings after hypohydration of 1%, 2% and 3% body mass induced by sauna exposure without exercise. No EAMC occurred in the nine participants in the control condition or after 1% dehydration; three subjects experienced EAMC in the 2%, and six subjects experienced EAMC in the 3% condition. In a study by Lau et al. (2019), 10 men ran downhill in a hot environment until they lost 2% of their initial body mass. Ten minutes after completing the run, they ingested either plain water or a commercially available oral hydration solution (ORS) containing sodium (50 mEq/L), chloride (50 mEq/L), potassium (20 mEq/L), magnesium sulphate (2 mEq/L), lactate (31 mEq/L), and glucose (18 g/L) in a volume equal to the mass lost. Susceptibility of the calf muscles to electrically induce cramp was assessed by a threshold frequency (TF) test applied at baseline before running, immediately after running, and 50 and 80 min after drink ingestion. Muscle cramp susceptibility assessed by TF did not change from baseline to immediately after running in either condition, but TF decreased after water intake by 4.3 Hz (at 30 min) and 5.1 Hz (at 60min post-run), but increased after ORS intake by 3.7 and 5.4 Hz, respectively. The investigators reported that serum sodium and chloride concentrations decreased after water intake but were maintained after ingestion of the electrolyte-containing drink.

In accord with the mechanisms proposed by Moss (1923), and others Anon (1920), these results suggest that the combination of sweat loss and water intake makes muscles more susceptible to cramps induced by electrical stimulation, but the susceptibility to muscle cramp decreases when a drink with a high electrolyte content is ingested. It is interesting to note that cramping is a recognized accompaniment of hyponatremia (defined as a serum sodium concentration less than 135 mmol/L) in clinical settings, but the extensive literature on exercise-associated hyponatremia, however, generally makes no mention of muscle cramping (Maughan & Shirreffs, 2019). The use of low-sodium dialysis fluids during maintenance dialysis may provoke cramping in renal patients, and normalization of plasma osmolality and sodium concentration can significantly reduce the frequency of cramping during dialysis (Meira et al., 2007). Whether this is relevant to the exercise situation, though, is uncertain.

EAMC as a Consequence of Altered Neuromuscular Control

The idea that cramp might be a consequence of events in the central nervous system (CNS), rather than in the muscles, is often portrayed as a novel idea (Schwellnus et al., 1997). However, a British parliamentary inquiry into the causes of muscle cramp in telegraph operators in 1911 concluded that “telegraphists’ cramp is a disease of the central nervous system, and is the result of a weakening or breakdown of the cerebral controlling mechanism in consequence of strain upon a given set of muscles.” (Departmental Committee on Telegraphists’ Cramp, 1911). This implicates events occurring in both the affected muscles and in the CNS but sheds no light on the pathways involved.

The early literature on muscle cramps was largely forgotten, and as evidence accumulated in the latter part of the last century that cramp often occurred during exercise in the absence of substantial sweat losses or gross disturbances in electrolyte balance, an alternative causation was sought. Schwellnus et al. (1997) hypothesized that cramp is caused by “sustained abnormal spinal reflex activity which appears to be secondary to muscle fatigue”. In particular, EAMC was ascribed to an abnormality of sustained motor neuron activity, due to an abnormality of motor neuron control at the spinal level, but this still does not identify the cause of this abnormality. Muscle fatigue was implicated through an excitatory effect on the muscle spindles (which are sensitive to muscle length) and an inhibitory effect on activity of the Type Ib Golgi tendon organs (which are sensitive to load). Circumstantial evidence in support of this suggestion arose from the observation that passive stretching of the muscle during an episode of cramp may alleviate the

symptoms, presumably as a result of an autogenic inhibition by the tendon organ reflex (Layzer et al., 1971). This still does not explain, though, why cramp is not an inevitable consequence of exercise that causes fatigue, why it appears to occur more frequently in environments that impose high thermal stress, or why some individuals are affected while others are not.

The strongest evidence for an altered neuromuscular control comes from laboratory studies of small muscles in humans and in animal models. In each of these two different scenarios, a story can be made, but in each case the story is incomplete. EAMC is notoriously unpredictable, so laboratory models have been developed to allow cramp to be induced more reliably, whether by voluntary activation of muscles or by electrically evoked contractions and in both cases, the muscle is activated while it is held in a shortened position. Various forms of this experimental model have been used in laboratory studies of cramping, even though this may not reflect the movement patterns of athletes. The results of these studies are consistent with the proposal of Schwellnus et al (1997) as outlined above: a reduction in the tension in the muscle tendon because of the shortening of the muscle will reduce the inhibitory feedback from the Golgi tendon organ, which in turn has the potential to increase the motor drive to the alpha motor neuron. In support of this hypothesis, Khan and Burne (2007) found that cramp induced by voluntary maximal activation of the gastrocnemius muscle while it was held in a shortened position could be inhibited by electrical stimulation of tendon afferents in the cramped muscle. Even under conditions that favored cramping, however, five of their 13 subjects could not induce cramping and in another two subjects, it did not persist long enough for measurements to be made.

Athletes who are prone to muscle cramps are reported to demonstrate a lower threshold for muscle cramps evoked by electrical stimulation of motor nerves (Miller & Knight, 2009; Minetto & Botter, 2009). Blocking of the motor nerves with local anesthetic does not abolish these electrically evoked cramps, but when the nerve is blocked, a greater stimulation frequency is required to induce cramping and cramp duration is reduced. Altered motor unit discharge characteristics are consistent with the existence of a positive feedback loop involving afferent input from affected muscles and motor drive to those muscles (Minetto et al, 2011).

Strong objections to the dehydration/electrolyte loss theory have been raised by studies that provided fluids to prevent dehydration and found that this did not affect the onset of electrically evoked cramps (Braulick et al., 2013; Miller et al., 2010b). These findings, however, are directly contradicted by other studies referred to above. It should also be noted that marked hypernatremia developed as a result of dehydration in the studies of Miller et al. (2010a) and Braulick et al. (2013), and this may have been protective against the development of cramp (Lau et al, 2019). Fatigue alone is also unlikely to be the cause, though it may be a contributing factor. In marathon runners, cramp tends to occur more frequently toward the end of races, and similar experiences are seen in football and other sports. However, everyone is fatigued to some extent in the later stages of endurance events, but relatively few experience muscle cramps. Furthermore, the nature of the fatigue that occurs in sprinters is very different from that experienced toward the end of a marathon race, but cramp may occur in either situation.

Rather than focusing on an either/or approach, therefore, it seems reasonable to suggest that different mechanisms may apply in different situations. We are all inevitably influenced by our own experiences and these may bias us toward one cause as being more likely or more common than another, but the key issue is how to treat or prevent an attack. With regard to treatment and prevention, it is important to note that a plausible mechanism can help to identify effective treatments but is not necessary to know if a treatment is effective or not.

PRACTICAL APPLICATIONS

The current state of knowledge in this field does not allow prescription of effective prevention and treatment strategies with any degree of certainty. The early studies of muscle cramping that occurred in industrial settings identified large sweat losses and ingestion of large volumes of plain water as factors contributing to muscle cramping, so it is not surprising that ingestion of salt was proposed as a prevention strategy. The strongest evidence for the efficacy of this strategy is found in the work of Dill et al. (1936), where large-scale prospective studies showed that addition of salt to drinking water was effective in reducing the rate of cramping. The recent study of Lau et al (2019) also provides support for this suggestion.

There is a long history of the use of folk remedies for the prevention and treatment of muscle cramps, and many of these have included compounds that have a strong or bitter taste, including pickle juice, mustard, quinine, vinegar, and various spices and herbs. Even homeopathic cures are reported to be effective, with anecdotal support from athletes often being used to promote these products, suggesting that both the placebo effect and athlete belief may play a powerful role. As with other interventions, these have proved difficult to evaluate as muscle cramps generally resolve spontaneously before any intervention can be implemented. In the human model of electrically invoked cramp, however, pickle juice (which has a high salt content and a sharp taste imparted by the acetic acid content) was reported to be effective in reducing the duration of cramps. Miller et al. (2010a) found that cramp duration was reduced by ~37% on average when 1 mL of pickle juice was ingested 2 s after induction of cramping compared with a trial where water was ingested (85 ± 19 s vs. 134 ± 16 s, respectively: $P < 0.05$), but the intensity of cramping was not affected. The same authors had previously shown that ingestion of small volumes of pickle juice had no measurable effect on plasma concentrations of sodium, potassium, magnesium or calcium concentration or on plasma osmolality and plasma volume (Miller et al., 2009). The authors proposed that, in the absence of any effect of the ingested pickle juice on circulating electrolyte concentrations, the mechanism by which pickle juice shortened cramp duration involved activation of receptors in the oropharyngeal region that resulted in a reduced firing rate of alpha motor neurons that innervate the affected muscle. It is important to note, though, that this was not a study of EAMC, but of cramping

induced by electrical stimulation during maximal voluntary contraction of a small muscle in the sole of the foot that was held in a shortened position. This cannot be taken as evidence of efficacy in the treatment of EAMC. However, this, and the results of other similar studies, raise some interesting questions: crossover designs involve using the same subjects in treatment and placebo trials, usually in the case of a single treatment, with half receiving treatment before placebo and the order reversed in the other half. The statistical analysis applied in the Miller et al. (2010a) study assumes that there was no treatment order effect, but we cannot be sure that this is true, with only one week for recovery between experimental trials. The authors of this and other studies involving similar experimental designs should have reported whether the cramp intensity and cramp duration were different between the first and second exposures, and should perhaps also have habituated the subjects to the electrical stimulation process prior to the experimental trials. The importance of this is highlighted by a recent publication showing that repeated exposures to electrically evoked cramps induce a long-lasting increase of the cramp threshold frequency (CTF) in healthy subjects (Behringer et al., 2018). These authors induced EAMC in the gastrocnemius medialis muscle of one leg twice a week, while the opposite leg served as the control leg. After four cramp training sessions, the CTF increased in the intervention leg but not in the control leg. This same consideration, of course, applies to many other laboratory studies of electrically evoked cramping, but becomes particularly acute when, as in the study of Miller et al. (2010b), a large difference between conditions occurs in the first trial, with possible consequences for the succeeding trial.

Another bitter tasting substance, quinine, has been promoted for the prevention of cramps, but there is little research specific to EAMC. A comprehensive review concluded that ingestion of quinine (200 mg to 500 mg daily) reduces cramp number and cramp days (low quality evidence) and reduces cramp intensity (moderate quality evidence) but has no effect on cramp duration (El-Tawil et al., 2015). They reported some evidence that ingestion of theophylline in combination with quinine improved cramp resistance more than quinine alone. A recently launched product has claimed that cramp can be prevented or treated by activation of transient receptor potential (TRP) in the mouth (Craighead et al., 2017), though this has not been supported by other research (Behringer et al, 2017). TRP receptors form a family of 28 related ion channels that are thought to be important for mediating the sensations of taste and pain. The TRPV1 and TRPA1 channels are stimulated by the active components of spicy foods such as chilli peppers or wasabi. It may be that evidence will emerge to support the product, but there are some questions about the science. There is no doubt that unpleasant (or pleasant) sensations in the mouth will induce electrical activity in some regions of the brain, but there are some gaps in the chain of events between stimulation of oropharyngeal receptors and the inhibition of activity in motor nerves. TRPV1 is activated by capsaicin if the local pH is less than 6 (Fernandes et al., 2012), but it is by no means certain that such a pH will be reached in the mouth after ingestion of this product. However, it is clear that ingestion of foods containing chilli, ginger and many other foods have powerful effects on receptors in the mouth and elsewhere. Anyone who has put raw chilli in their mouth or near their eye will be aware that this causes not only pain and irritation but also a variety of physiological responses. Whether these signals can disrupt the electrical activity associated with spontaneous muscle cramps remains uncertain.

SUMMARY

- Muscle cramp is relatively common in many exercise situations, but the causes are not well understood, making prevention and treatment strategies uncertain.
- Some cramps are associated with disturbances of water and salt balance and taking care to minimize such disturbances should reduce the risk.
- When water and salt losses are high, drinks containing electrolytes, especially sodium, should be taken rather than plain water. Under-hydration and over-hydration should be avoided.
- Stretching the affected muscles may speed resolution of cramps.
- No prevention strategy or treatment is consistently effective. Trial and error may help to establish effective procedures.

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