The Influence of High-Voltage Electrical Stimulation on Edema Formation After Acute Injury: A Systematic Review

Alison R. Snyder, April L. Perotti, Kenneth C. Lam, and R. Curtis Bay

Context: Electrical stimulation is often used to control edema formation after acute injury. However, it is unknown whether its theoretical benefits translate to benefits in clinical practice. Objectives: To systematically review the basic-science literature regarding the effects of high-voltage pulsed stimulation (HVPS) for edema control. Evidence Acquisition: CINAHL (1982 to February 2010), PubMed (1966 to February 2010), Medline (1966 to February 2010), and SPORTDiscus (1980 to February 2010) databases were searched for relevant studies using the following keywords: edema, electrical stimulation, high-volt electrical stimulation, and combinations of these terms. Reference sections of relevant studies were hand-searched. Included studies investigated HVPS and its effect on acute edema formation and included outcome measures specific to edema. Eleven studies met the inclusion criteria. Methodological quality and level of evidence were assessed for each included study. Effect sizes were calculated for primary edema outcomes. Evidence Synthesis: Studies were critiqued by electrical stimulation treatment parameters: mode of stimulation, polarity, frequency, duration of treatment, voltage, intensity, number of treatments, and overall time of treatments. The available evidence indicates that HVPS administered using negative polarity, pulse frequency of 120 pulses/s, and intensity of 90% visual motor contraction may be effective at curbing edema formation. In addition, the evidence suggests that treatment should be administered in either four 30-min treatment sessions (30-min treatment, 30-min rest cycle for 4 h) or a single, continuous 180-min session to achieve the edema-suppressing effects. Conclusions: These findings suggest that the basic-science literature provides a general list of treatment parameters that have been shown to successfully manage the formation of edema after acute injury in animal subjects. These treatment parameters may facilitate future research related to the effects of HVPS on edema formation in humans and guide practical clinical use.

Keywords: electrotherapy, acute edema, inflammation, edema prevention, treatment efficacy
The management of acute injuries is one of the primary responsibilities of a sport rehabilitation clinician. It is theorized that immediate and proper medical care of an acute injury can shorten recovery periods and, subsequently, return patients back to play faster.\(^1\) A key objective of acute injury management is limiting edema formation after trauma. Uncontrolled accumulation of edema at the injury site can be troubling for both the patient and the clinician because it is often difficult to eliminate once present in the affected area and is typically associated with an increase in pain, impaired function, and prolonged recovery.\(^2\) Although there are various interventions aimed at curbing edema formation after injury (eg, compressive devices, therapeutic exercise), a common clinical approach to edema control is the use of high-voltage pulsed stimulation (HVPS).

HVPS is a form of electrical stimulation characterized by a monophasic current and a known polarity of the electrodes (ie, positive, negative).\(^3\) There are several theories that address the potential effects of HVPS on edema formation. From a physiological standpoint, edema formation is related to a leakage of plasma proteins in cell membranes into interstitial spaces after injury, resulting in an increase in fluid accumulation in the affected area.\(^1\) It is theorized that HVPS minimizes the leakage of plasma proteins and, thus, edema formation by limiting microvascular permeability (ie, decreasing permeability between cell membranes and interstitial spaces)\(^4\) and repelling large, negatively charged plasma proteins from interstitial spaces through the placement of a negatively charged electrode over the injury site.\(^5-7\) Another theory suggests that HVPS can decrease edema by increasing the rate of plasma protein uptake through lymphatic channels, which, in turn, leads to an increase in the uptake of accumulated fluids through the lymphatic system.\(^2\) Although it is based on a sound rationale, the efficacy and effectiveness of HVPS on edema control after an acute injury remain unclear.

Only 2 studies have investigated the potential effects of HVPS on edema formation in human subjects.\(^8,9\) The limited number of studies, as well as their methodological variability, makes it difficult to develop a general consensus of the optimal treatment parameters for the clinical use of HVPS. Conversely, there have been numerous basic-science studies investigating the effects of HVPS on edema formation in frog and rat subjects. Although their findings may not be directly transferable to human patients, these studies offer insight into the potential treatment effects of HVPS on edema control and potential treatment parameters that have implications for future human investigations and practical clinical use. Therefore, a systematic review of the available basic-science literature is necessary to elucidate potential HVPS treatment parameters that warrant further investigation through clinical research.

**Objective**

The objective of this study was to systematically review the basic-science literature regarding the effects of HVPS for edema control. The aims of this review were to evaluate the efficacy of HVPS for edema control after an acute injury in animal subjects and identify potential treatment parameters to be considered for research in human subjects and clinical practice in sport rehabilitation.
Evidence Acquisition

Study Search
Studies were screened by titles and abstracts by 3 independent investigators (A.R.S., A.P., K.C.L.) and were selected for the review if they met the following criteria: (1) They investigated the effects of sensory-level HVPS on the prevention or treatment of edema formation after acute trauma, (2) they used limb volume as an outcome measure, (3) they used an animal-model methodology, (4) they were written in English, and (5) they were published in a peer-reviewed journal. Additional studies were identified by reviewing the reference lists of all relevant studies. In February 2010, a literature search was performed using CINAHL (1982 to February 2010), PubMed (1966 to February 2010), Medline (1966 to February 2010), and SPORTDiscus (1980 to February 2010). Keywords included edema, electrical stimulation, electrical stimulation therapy, high voltage electrical stimulation, and high volt electrical stimulation. Endnote (Thomson, version 9, © 2005) was used to record and manage all referenced studies.

Assessment of Methodological Quality and Level of Evidence
To evaluate the design quality across all selected studies, 2 investigators (A.R.S., K.C.L.) used criteria based on Sackett’s levels of evidence and previously described by Lieberman and Scheer to rate each study. Each study was graded on research design, sample size, internal validity, and external validity. Internal validity was based on an evaluation of several factors such as reliability testing of instrumentation, blinding of measurement rater, restriction of movement between treatment sessions, and confirmation of injury (ie, edema formation, not frank bleeding). Based on these criteria, a grade ranging from IA1a (strongest evidence) to IVB3c (weakest evidence) was given to each study.

Data Extraction
Means, standard deviations, and sample sizes were extracted or calculated for all included studies. These values were subsequently used for evaluation purposes.

Statistical Analysis
Standardized effect sizes (Cohen’s $d$) were hand-calculated for the primary results of all included studies based on the data provided by each study (eg, graphs, means, standard deviations) and were determined by dividing the difference between the mean values of the control group and treatment group by the pooled standard deviation of the 2 groups. Thus, a positive effect size indicated a beneficial treatment effect of HVPS in curbing edema formation, and the magnitude of the effect was interpreted as trace ($<.2$), small ($0.2–.49$), medium ($0.5–.79$), or large ($>.80$). Ninety-five-percent confidence intervals around the standardized effect sizes were also computed.
Evidence Synthesis

Study Selection

The literature search resulted in identification of 32 relevant studies, 11,6,13–22 of which met our specified inclusion criteria and were included in this systematic review. Twenty-one studies2,4,7–9,23–38 were excluded from this review for reasons such as administration of stimulation treatments that were not HVPS, treatment of chronic edema, lack of edema as an outcome measure, and use of motor-level stimulation.

Overview of Included Studies

Tables 1 and 2 outline the demographics and characteristics, respectively, of all included studies.

Methods of Trauma Induction

Ten6,14–22 of the 11 included studies used a crush protocol to induce injury in subjects (Table 1). Only Bettany et al13 reported a different protocol, in which the ankles of frog subjects were slowly hyperflexed to 90° by a motor-driven device. The crush protocol for all other studies was introduced by Bettany et al14 and subsequently adapted by Mendel et al6 for rat studies. In general, the crush protocol for the frog studies consisted of dropping a 450-g steel rod through a vertical tube from a height of 1.1 m onto the plantar aspect of the limb. A rectangular piece of wood was placed between the tube and limb to evenly distribute the resultant force and prevent the

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of evidence</th>
<th>Number of subjects</th>
<th>Injury type</th>
<th>Body part</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frog studies</td>
<td></td>
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<tr>
<td>Bettany et al13</td>
<td>IA2c</td>
<td>20</td>
<td>hyperflexion</td>
<td>ankles</td>
</tr>
<tr>
<td>Bettany et al14</td>
<td>IA1c</td>
<td>20</td>
<td>crush</td>
<td>hind limb</td>
</tr>
<tr>
<td>Fish et al19</td>
<td>IB1c</td>
<td>14</td>
<td>crush</td>
<td>hind limb</td>
</tr>
<tr>
<td>Taylor et al21</td>
<td>IA1c</td>
<td>24</td>
<td>crush</td>
<td>hind limb</td>
</tr>
<tr>
<td>Rat studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cosgrove et al15</td>
<td>IB3c</td>
<td>44</td>
<td>crush</td>
<td>hind limb</td>
</tr>
<tr>
<td>Dolan et al16</td>
<td>IB2c</td>
<td>21</td>
<td>crush</td>
<td>hind limb</td>
</tr>
<tr>
<td>Dolan et al17</td>
<td>IB1c</td>
<td>22</td>
<td>crush</td>
<td>hind limb</td>
</tr>
<tr>
<td>Dolan et al18</td>
<td>IB1c</td>
<td>34</td>
<td>crush</td>
<td>hind limb</td>
</tr>
<tr>
<td>Mendel et al6</td>
<td>IB2c</td>
<td>20</td>
<td>crush</td>
<td>hind limb</td>
</tr>
<tr>
<td>Mohr et al20</td>
<td>IA3c</td>
<td>40</td>
<td>crush</td>
<td>hind limb</td>
</tr>
<tr>
<td>Thornton et al22</td>
<td>IB1c</td>
<td>44</td>
<td>crush</td>
<td>hind limb</td>
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</tbody>
</table>
# Table 2  Study Characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Control</th>
<th>Frequency (pps)</th>
<th>Polarity</th>
<th>Intensity</th>
<th># of sessions</th>
<th>Treatment duration (min)</th>
<th>Edema outcome</th>
</tr>
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<tbody>
<tr>
<td><strong>Frog studies</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bettany et al(^{13})</td>
<td>HVPS</td>
<td>no HVPS</td>
<td>120</td>
<td>–</td>
<td>90% VMT</td>
<td>4</td>
<td>30</td>
<td>+</td>
</tr>
<tr>
<td>Bettany et al(^{14})</td>
<td>HVPS</td>
<td>no HVPS</td>
<td>120</td>
<td>–</td>
<td>90% VMT</td>
<td>4</td>
<td>30</td>
<td>+</td>
</tr>
<tr>
<td>Fish et al(^{19})</td>
<td>HVPS</td>
<td>no HVPS</td>
<td>120</td>
<td>+</td>
<td>90% VMT</td>
<td>4</td>
<td>30</td>
<td>No difference</td>
</tr>
<tr>
<td>Taylor et al(^{21})</td>
<td>HVPS</td>
<td>no HVPS</td>
<td>120</td>
<td>–</td>
<td>90% VMT</td>
<td>1</td>
<td>30</td>
<td>+</td>
</tr>
<tr>
<td><strong>Rat studies</strong></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cosgrove et al(^{15})</td>
<td>HVPS</td>
<td>sham</td>
<td>100</td>
<td>–</td>
<td>90% VMT</td>
<td>3</td>
<td>60</td>
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<tr>
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<td>HVPS</td>
<td>no HVPS</td>
<td>120</td>
<td>–</td>
<td>90% VMT</td>
<td>1</td>
<td>180</td>
<td>+ HVPS</td>
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<td></td>
<td>HVPS + IBU</td>
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<td></td>
<td></td>
<td></td>
<td>+ HVPS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>+ HVPS + IBU</td>
</tr>
<tr>
<td>Dolan et al(^{17})</td>
<td>HVPS</td>
<td>no HVPS</td>
<td>120</td>
<td>–</td>
<td>90% VMT</td>
<td>4</td>
<td>30</td>
<td>No group differences</td>
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<tr>
<td></td>
<td>CWI</td>
<td></td>
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<td></td>
<td>+ HVPS</td>
</tr>
<tr>
<td></td>
<td>HVPS + CWI</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ HVPS + CWI</td>
</tr>
<tr>
<td>Dolan et al(^{18})</td>
<td>HVPS</td>
<td>no HVPS</td>
<td>120</td>
<td>–</td>
<td>90% VMT</td>
<td>1</td>
<td>180 HVPS or CWI</td>
<td>+ HVPS</td>
</tr>
<tr>
<td></td>
<td>CWI</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ CWI</td>
</tr>
<tr>
<td></td>
<td>HVPS + CWI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No group differences</td>
</tr>
<tr>
<td>Mendel et al(^{16})</td>
<td>HVPS</td>
<td>no HVPS</td>
<td>120</td>
<td>–</td>
<td>90% VMT</td>
<td>4</td>
<td>30</td>
<td>+</td>
</tr>
<tr>
<td>Mohr et al(^{20})</td>
<td>HVPS</td>
<td>no HVPS</td>
<td>80</td>
<td>–</td>
<td>40 V (no VMC)</td>
<td>3</td>
<td>20</td>
<td>No difference</td>
</tr>
<tr>
<td>Thornton et al(^{22})</td>
<td>HVPS</td>
<td>no HVPS</td>
<td>120</td>
<td>–</td>
<td>90% VMC</td>
<td>4</td>
<td>30</td>
<td>+ (2 of 3 rat strains)</td>
</tr>
</tbody>
</table>

pps, pulses/s; HVPS, high-voltage pulsed stimulation; VMT, visual motor threshold; IBU, ibuprofen; CWI, cold-water immersion; VMC, visual motor contraction.
skin from rupturing.\textsuperscript{14} Rat studies used a slightly modified protocol because of the anatomical differences between rats and frogs. The protocol consisted of dropping an 85.5-g weight through a vertical tube from a height of 30 cm onto the limb. A piece of plastic was placed between the tube and limb to ensure that the trauma did not result in damage to major vessels.\textsuperscript{6}

To confirm that limb-volume changes were caused by edema formation and not frank bleeding, investigators either made skin incisions on the involved limb just before the animal’s sacrifice (frogs and rats)\textsuperscript{6,13,14,16–19,21} or viewed the injury through the animal’s translucent skin (rats).\textsuperscript{22} If it was determined that a subject suffered a more significant injury, investigators excluded the subject from data analysis. Two studies\textsuperscript{15,20} did not mention any confirmatory procedures.

### Treatment Parameters

Treatment parameters across all included studies are outlined in Table 2. The most commonly investigated HVPS treatment protocol (45\%)\textsuperscript{5,13,14,17,22} was four 30-minute treatments (30-min treatment, 30-min rest cycles for 4 h) with a negative polarity over the injury site at a frequency of 120 pulses/s (pps) and an intensity of 90\% visual motor contraction. Other studies \((n = 6)\textsuperscript{6,15,16,18,20,21}\) reported variations in frequency, polarity, intensity, treatment session, or treatment duration.

### Methodological Quality and Level of Evidence

The grading for methodological quality and level of evidence for all included studies is listed in Table 1. All grades were consistent between the 2 raters. Two studies\textsuperscript{14,21} (18\%) received a rating of IA1c, indicating that their findings represent the strongest available evidence in the current basic-science literature. Of the remaining studies, 1 study\textsuperscript{13} (9\%) received a rating of IA2c, 1 study\textsuperscript{20} (9\%) received IA3c, 4 studies\textsuperscript{17–19,22} (36\%) received IB1c, 2 studies\textsuperscript{6,16} (18\%) received IB2c, and 1 study\textsuperscript{15} (9\%) received IB3c.

### Data Synthesis

Effect sizes and 95\% confidence intervals for frog studies, short-duration rat studies, and long-duration rat studies are depicted in Figures 1, 2, and 3, respectively.

### Frog Studies

Bettany et al\textsuperscript{13,14} used the same treatment protocol (four 30-min treatments with a negative polarity over the injury site at a frequency of 120 pps and an intensity of 90\% visual motor contraction) on 2 types of injuries (crush and hyperflexion). Despite differences in the type of injury, both studies demonstrated medium and large effect sizes that favored HVPS for edema control over the first 24 hours post-trauma. In contrast, Taylor et al\textsuperscript{21} showed small and medium effect sizes that favored HVPS for edema control during the initial 8 hours posttrauma but trace effect sizes at 17, 20, and 24 hours posttrauma. The apparent discrepancy in the trend of effect sizes over time between the investigations may be related to
Figure 1 — The magnitude of the treatment effect for high-voltage pulsed stimulation on limb volume in frog studies during the first 24 hours posttrauma. Larger effect sizes indicate a larger treatment effect. The dotted line represents a standardized effect size of .62. Standardized effect sizes above the dotted line had significant 95% confidence intervals (ie, confidence interval did not include zero).
Figure 2 — The magnitude of the treatment effect for high-voltage pulsed stimulation on limb volume in rat studies during the first 4 hours post-trauma. Larger effect sizes indicate a larger treatment effect. The dotted line represents a standardized effect size of .62. Standardized effect sizes above the dotted line had significant 95% confidence intervals (i.e., confidence interval did not include zero).
Figure 3 — The magnitude of the treatment effect for high-voltage pulsed stimulation on limb volume in rat studies during the first 96 hours post-trauma. Larger effect sizes indicate a larger treatment effect. The dotted line represents a standardized effect size of .62. Standardized effect sizes above the dotted line had significant 95% confidence intervals (i.e., confidence interval did not include zero).
differences in the number of treatment sessions. Although the studies used identical stimulation parameters, Taylor et al\textsuperscript{21} only performed 1 treatment session, and the other 2 studies\textsuperscript{13,14} performed 4 sessions. The findings of and differences between these studies suggest that multiple treatment sessions may play a role in prolonging the effects of HVPS on edema control during the first 24 hours posttrauma.

Only 1 investigation\textsuperscript{19} examined the effects of using a positive polarity over the injury site during the initial 2 hours immediately after trauma. The results of that study demonstrated only trace effect sizes during the initial hours posttrauma, suggesting that positive polarity may not be as effective in curbing edema formation as negative polarity. However, it should be noted that studies using the same treatment protocol but implementing a negative polarity over the injury site\textsuperscript{13,14} showed a gradual increase in effect sizes over time, particularly between 3 and 24 hours posttrauma. The trend of increasing effect sizes implies that the effects of HVPS may take longer than 2 hours to manifest and suggests that Fish et al\textsuperscript{19} may not have carried out their measurements long enough to observe the potential effects of HVPS with positive polarity on edema control.

**Rat Studies**

Dolan et al,\textsuperscript{17} Mendel et al,\textsuperscript{6} and Thornton et al\textsuperscript{22} used the same treatment protocol as Bettany et al.\textsuperscript{14} Dolan et al\textsuperscript{17} demonstrated medium and large effect sizes that generally increased over time and favored HVPS for edema control across the first 4 hours posttrauma. In contrast, Mendel et al\textsuperscript{6} demonstrated medium and large effect sizes during the initial 1.5 hours posttrauma but then showed a gradual decrease to small effect sizes 2 to 4 hours posttrauma. The contrast in the effect-size trend between these studies may be a result of the different rat species used by the investigators; Dolan et al used all Zucker lean (n = 22) rats and Mendel et al used a combination of Zucker lean (n = 18) and Sprague Dawley (n = 6) rats. The potential influence of rat species on the effects of HVPS is highlighted by a study\textsuperscript{22} that demonstrated medium and large effect sizes for Zucker lean and Brown Norway rats but small to medium effect sizes for Sprague Dawley rats while using an identical stimulation treatment protocol for all 3 species. These findings support the need for further investigations into the use of stimulation in the population of interest, including humans.

The remaining rat studies incorporated different stimulation parameters in their protocols. In their other studies, Dolan et al\textsuperscript{16,18} used the same stimulation setup as Bettany et al\textsuperscript{14} but performed a single, continuous 180-minute treatment session as opposed to four 30-minute sessions. In both of those studies an effect of stimulation was found during the first 4 hours posttrauma, with 1 study demonstrating large effects over time and the other producing small to large effects. These findings suggest that a single, continuous 180-minute treatment session may produce results comparable to those of four 30-minute treatment sessions,\textsuperscript{13,14} especially when one is interested in curbing edema formation in the first 24 hours posttrauma.

Other studies\textsuperscript{15,20} recorded limb measurements after the initial 24 hours post-trauma and reported trace\textsuperscript{15} and medium\textsuperscript{20} effect sizes. These findings suggest that, on a long-term basis, HVPS may not control edema formation and in some cases suggest that doing nothing is more beneficial. However, it should be noted
that 1 study used a frequency of 100 pps and three 60-minute treatment sessions, and the other study used a frequency of 80 pps, as suggested by the stimulator manufacturer, with an intensity of 40 V and three 20-minute treatment sessions. In addition, those investigators did not record any measurements during the first 24 hours posttrauma, a time period in which other studies have shown large effect sizes in favor of HVPS for edema control. In light of this, it is difficult to determine whether the HVPS treatment administered in these investigations lost effectiveness over time or the implemented treatment parameters or methods were ineffective at producing a measureable change in edema formation. For example, 1 of these studies administered 60-minute treatments whereas other studies have reported benefits after four 30-minute or one 180-minute treatment, so differences may be a result of treatment duration. Voltage is another consideration; stimulation delivered at 40 V is arbitrary, as indicated by the authors, and may produce a submotor or subsensory effect depending on the subjects, making it possible that the stimulation parameter produced different effects across the treatment group. In addition, some investigations did not limit animal movement between treatment periods, which may have affected edema formation by allowing animals to move (eg, drag) or attend to the injured limb (eg, rub or lick).

Discussion

The objective of this study was to systematically review the basic-science literature to evaluate the efficacy of HVPS for edema control after an acute injury and to identify potential treatment parameters warranting consideration for research in human subjects and clinical practice in sport rehabilitation. This review revealed trace to large HVPS treatment effects for edema control after an acute injury in several different animal models, indicating that HVPS may be an appropriate and efficacious modality for the treatment of acute edema formation. It is not surprising that factors such as polarity, frequency, voltage, number and timing of treatment sessions, treatment duration, and animal species can influence the effects of HVPS on edema control. However, when considering reported effect sizes and methodological quality, the best available evidence indicates that HVPS administered in negative polarity at a pulse frequency of 120 pps and an intensity of 90% visual motor contraction may be an effective approach to curbing edema formation. The evidence also suggests that treatment should be administered in four 30-minute treatment sessions (30-min treatment, 30-min rest cycle for 4 h) or a single, continuous 180-minute session to optimize the beneficial effects of HVPS for edema control. In addition, based on the available evidence, it appears that treatments should be delivered early and often or for long durations after injury to gain the most benefit in terms of edema control. In light of this evidence, these treatment parameters (Table 3) offer guidelines for human-research studies, as well as clinical use in sport rehabilitation.

As is the case with all systematic reviews, conclusions are limited by the quality and extent, as well as the heterogeneity, of data from primary research studies. We have noted the methodological quality of the trials included and cited commonalities and differences among them. Although the data are somewhat sparse, we believe they are sufficient to provide useful guidelines and starting points for research in human subjects.
Currently, there is limited evidence in human subjects regarding the effectiveness of HVPS in curbing edema formation after acute injury. To our knowledge, only 2 human studies have investigated the effects of HVPS on edema formation (as measured by limb volume). One study examined the effects of ice and HVPS on ankle limb volume after grades I and II ankle sprains. Subjects were randomly assigned to receive either 30-minute treatments of ice, ice and HVPS at 28 pps, or ice and HVPS at 80 pps once a day for 3 days. Compression wraps and crutches were also used on all subjects. The findings suggest a variable response to electrical stimulation used to curb edema in those suffering acute musculoskeletal injury, which is demonstrated by trace to large effects in both pulse-frequency conditions. However, that study was weakened by large amounts of error associated with their measurements (eg, volumetric measurement system) and standardized effect-size confidence intervals that crossed zero, lessening the implications of their results. The other investigation reported similar, nonsignificant findings while investigating the effects of sensory-level monophasic high-voltage stimulation on arm-limb volume after acute injury to the forearm flexors. Thirty-minute stimulation treatments were administered immediately after injury and at 3, 5, 24, 48, 72, 96, and 120 hours postinjury at a frequency of 120 pps and a negative polarity. The results of the investigation indicated both small (.27) and medium (–.54) effect sizes immediately after stimulation treatments. Moreover, the medium negative effect size, though not significant, is concerning because this trend suggests that a larger effect may result when no treatment is delivered. However, and similar to the other human studies, large amounts of error associated with the limb-volume measurement and standardized effect-size confidence intervals that crossed zero limit the meaningfulness of these findings.

In addition, the human investigations were conducted somewhat differently in relation to methodology, including mechanism of injury, and treatment parameters than the basic-science research that used animals as subjects. These variations warrant evaluation so that future clinical research using humans as subjects may be constructed using the same parameters shown promising in basic-science research. Most of the animal studies induced trauma by crush injury, which is similar to a contusion in humans. One investigation used forced lengthened contractions to induce muscle strain and the other was conducted on military recruits with lateral ankle sprains. Ligament and muscle injuries are different from contusions, so the

### Table 3 Recommendations for Controlling Acute Edema Formation With High-Voltage Pulsed Stimulation

<table>
<thead>
<tr>
<th>Stimulation parameter</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Frequency</td>
<td>120 pulses/s</td>
</tr>
<tr>
<td>Polarity</td>
<td>Negative</td>
</tr>
<tr>
<td>Intensity</td>
<td>90% visual motor threshold</td>
</tr>
<tr>
<td>Treatment protocol</td>
<td>4 sessions (30-min treatment, 30-min rest cycle) or 1 session (180-min continuous treatment)</td>
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</table>
effects of stimulation measured in animals may be different simply because of the injury protocols.

A notable inconsistency between basic-science and human studies is the specific stimulation treatment parameters evaluated. Almost all the animal studies used similar treatment protocols for frequency, intensity, and mode of application. The 2 human studies used different treatment parameters. One human investigation used 2 different frequencies of stimulation, 28 and 80 pps, that are not the frequency previously used and shown to be effective in animal investigations (120 pps). However, the investigators selected these parameters based on printed protocols for their stimulation unit. Differences also occurred in the mode of stimulation, with 1 human study using HVPS delivered on the skin surface, without the use of water immersion. Lack of application through water may be a factor because water immersion was found to be beneficial in several animal investigations. Michlovitz and Watkins used ice placed circumferentially around the treatment area, again differing from the mechanism of application used in the animal studies. Finally, neither of the human studies determined stimulation intensity through identification of the 90% voluntary muscle-contraction level that was used in the animal investigations. Therefore, it is possible that the human subjects received a different level of stimulation than the animals, resulting in a different outcome. Because of the variability in frequency, intensity, and mode of application used between the animal and human studies, future human investigation may be better designed using the parameters identified as potentially favorable in animal studies for curbing edema after acute injury.

Another variation in treatment between animal and human studies was the duration and number of stimulation treatments delivered. In the animal studies, the amount of stimulation delivered influenced the treatment outcome, with four 30-minute treatments or a single longer-duration treatment (3 hours) retarding edema formation. One human study only administered single 30-minute stimulation treatments that began within 30 hours of the injury. If timing of the stimulation is important, as indicated by the animal investigations and suggested by others, the long time delay between the injury and initiation of stimulation treatment may influence the outcome, affecting the impact of the treatment on edema formation. Although the other human investigation administered several treatments on the first day of injury, including 1 immediately postinjury, there were long rest periods between the remaining 5 treatments (ie, approximately 24 hours), which may have affected the efficacy of the treatment. However, the use of longer rest periods between treatments may be more similar to what actually occurs in clinical practice. In clinical practice, it is common for stimulation treatments to be administered to patients once a day for a duration of about 20 minutes. In addition, patients may only receive stimulation treatments a couple of times during the week, especially if being treated in a clinic setting. The implementation of multiple treatments each day is less common, as is the application of stimulation for periods as long as 3 hours. As a result of these practice characteristics, it is unlikely that most patients will be able to receive stimulation treatments several times a day or for several hours at a time, as can be arranged when using laboratory animals as subjects. The issue of number and duration of treatments appears to be a significant factor in the successful use of electrical stimulation, although the parameters identified as favorable in the basic-science literature may be unrealistic in clinical practice. More
research on the impact of single, short-duration treatments is needed to determine whether the more typical 1-treatment-per-day practice provides any clinical benefit in terms of edema reduction.

Finally, although our primary aim was to evaluate the impact of only HVPS on edema formation, several animal studies have investigated whether there is an additive effect of stimulation when combined with other treatments (Table 2).\textsuperscript{16–18} Combination treatments are often used clinically, and in animal models specific attention has been given to cold-water immersion and ibuprofen. Results of these studies have shown that these other treatments, whether given alone or in combination with stimulation, produce similar outcomes. That is, all treatments limit the formation of edema in the treatment limbs compared with the control limbs, but there is no difference in effect between the various treatments. These findings indicate that cold-water immersion, HVPS, and ibuprofen were equally efficacious and had no additive effect when combined.\textsuperscript{16,17,27} Consequently, if there is no difference in treatment outcome, then perhaps the decision of which modality or therapy to use should be based on criteria such as cost, ease of use, patient preference, and clinician and patient time constraints.\textsuperscript{16,17,27} For example, patients may prefer a mixture of therapies, such as alternating cold-water immersion and stimulation treatments. Future research should investigate whether alternating treatments changes the impact on acute edema formation. In addition, if an insurance company does not reimburse for stimulation treatments, cold-water immersion may be a better financial option for the patient.

The basic-science research findings have assisted in determining a general set of treatment parameters including mode of administration, polarity, voltage, and number and duration of treatments that positively influence the outcome of HVPS used to manage acute edema formation (Table 3). However, there remains a lack of investigation into the effects of HVPS for the purposes of curbing edema formation in humans who have suffered acute injury. Because the available human studies did not incorporate the exact parameters used in the animal investigations, it is not possible to determine whether these same parameters are effective in humans or clinical practice. Studies that translate the identified efficacious stimulation parameters from animal research to the human model would benefit the field of sport rehabilitation. Future investigations with human subjects should use the parameters shown to be effective, or most favorable, through basic-science research because they may be the most appropriate for identifying positive treatment outcomes and the clinical usefulness of this modality in treating edema after acute injury.

**Conclusion**

There is a need for research supporting the practices of rehabilitation medicine. Although health care professionals frequently use electrical muscle stimulation in the treatment of acute injuries, there are surprisingly few studies addressing the effects of specific stimulation treatments. Lack of investigation evaluating the efficacy and effectiveness of HVPS in the treatment of acute injuries should raise questions about the usefulness of stimulation as a treatment modality for these conditions. The findings from this systematic review indicate that, based on the best available evidence from basic-science research, it is possible to limit edema formation after acute injury. In addition, basic-science research suggests that there are
general stimulation parameters that appear to produce the best outcome in treating acute edema formation. The many differences in study design and characteristics of the animal and human studies highlight the need for standardized parameters when conducting modality research. Future studies investigating the therapeutic effects of electrical stimulation in humans are needed and should use the parameters identified in the basic-science research as guidelines for designing clinical research.

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