Miniature Electrical Stimulator for Hemorrhage Control

Mark R. Brinton, *Student Member, IEEE*, Yossi Mandel*, Roopa Dalal, and Daniel Palanker

***Abstract*—Noncompressible hemorrhage is currently the most common cause of preventable death in battlefield and in civilian trauma injuries. Tourniquets, specialized wound dressings, and hemorrhage-inhibiting biomaterials are not sufficiently effective in arrest of noncompressible hemorrhage and often cause collateral tissue damage. An effective, easy-to-use, portable device is needed to reduce blood loss in trauma patients immediately following injury and to maintain hemorrhage control up to several hours—until the injured is evacuated to a medical facility. We developed a miniature electrical stimulator to induce vascular constriction and, thereby, reduce hemorrhage. Vasoconstriction of the rat femoral arteries and veins was studied with pulse durations in the range of 1 μs to 10 ms and repetition rate of 10 Hz. Pulse amplitude of 20 V, duration of 1 ms, and repetition rate of 10 Hz were found sufficient to induce rapid constriction down to 31 $\pm$ 2% of the initial diameter, which could be maintained throughout a two-hour treatment. Within one minute following treatment termination the artery dilated back to 88 $\pm$ 3% of the initial diameter, providing rapid restoration of blood perfusion. Histology indicated no damage to the vessel wall and endothelium seven days after stimulation. The same treatment reduced the blood loss following complete femoral artery resection by 68 $\pm$ 11%, compared to untreated vessels. Very low power consumption during stimulation ($<$10 mW per 1.6 mm electrode) allows miniaturization of the stimulator for portable battery-powered operation in the field to control the blood loss following vascular trauma.**

***Index Terms*—Electrical stimulation, hemorrhage control, junctional bleeding, vascular trauma, vasoconstriction.**

I. Introduction

HEMORRHAGE shock is the second leading cause of fatality among those traumatically injured in the United States, accounting for 30%–40% of trauma deaths [1]. Hemorrhage control is especially challenging in cases of junctional areas, such as inguinal hemorrhage, and hemorrhage in internal solid organs, such as the liver and spleen. Hemorrhage from these areas cannot be successfully controlled using traditional tourniquets or standard bandages. According to the U.S. military reports, successful implementation of traditional tourniquets significantly reduced hemorrhage morbidity from limb injury, and now hemorrhage not amenable to truncal tourniquets (i.e., noncompressible wounds in joints, cavities, and solid organs) is the most common cause of preventable of death [2]–[4].

Recent military data from U.S. and coalition troops reports that 23% of casualties were potentially survivable, 20% of which died from junctional hemorrhage [3]. Consequently, an efficient method of hemostasis could have prevented these casualties. A device capable of preventing hemorrhage from truncal noncompressible injuries could save an even greater number of lives [4].

Recent efforts to address the problem of noncompressible hemorrhage include use of hemorrhage-inhibiting biomaterials, gauze packing, or sophisticated new tourniquets. Biomaterials and biomaterial-enhanced dressings have been proven effective for some locations and severity of injury, but not all [5]. For example, wound dressings enhanced with fibrin, chitosan (HemCon), or poly(N-acetyl glucosamine) have inhibited hemorrhage with high efficacy. However, they are less effective when applied to deep cavity or incompressible wounds [5]–[7]. Similarly, the QuikClot Combat Gauze, a zeolite-based wound dressing endorsed by the US Army for hemorrhage control not amenable to a tourniquet, and other enhanced wound dressings, are also ineffective in junctional bleeding (i.e., groin, gluteal, axilla, shoulder, and others) [1], [3], [5], [8], [9]. In a powdered form, biomaterials such as QuikClot granules can be easily poured into deep wounds and conform to irregular surfaces but can cause tissue damage by exothermic reactions, may have local or systemic toxicity, and are not biodegradable and, therefore, must be removed before definitive surgery [5]. WoundStat, a ceramic-based hemostatic powder, was shown to be more effective than QuikClot granules and HemCon dressing in a porcine femoral artery model [10]. Unfortunately, WoundStat was difficult to remove from the wounds and it caused endothelial damage and moderate vein necrosis [10]. Recently, improved control of noncompressible solid organ hemorrhage has been achieved using a polyurethane injection. However, this technique can only be used with closed cavity injuries, and tissue necrosis was observed as a result of the pressure increase within the cavity [11]. A new tourniquet, the Combat Ready Clamp (CRoC), approved by the FDA for prehospital hemorrhage control, can only be used for inguinal hemorrhage and cannot be applied to the head, neck, abdomen, and chest [12], [13]. Animal and cadaver studies indicated the

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M. R. Brinton is with the Electrical Engineering Department, Stanford University, Stanford, CA 94305 USA (e-mail: mbrinton@stanford.edu).

*Y. Mandel was with the Stanford University, Stanford, CA 94305 USA. He is now with the Faculty of Life Sciences, Bar Ilan University, 52900 Ramat Gan, Israel (e-mail: yossi.mandel@gmail.com).

R. Dalal is with the Department of Ophthalmology, Stanford School of Medicine, Stanford University, Stanford, CA 94305 USA (e-mail: roopa_dalal@hotmail.com).

D. Palanker is with the Department of Ophthalmology and the Hansen Experimental Physics Laboratory, Stanford University, Stanford, CA 94305 USA (e-mail: palanker@stanford.edu).

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CRoC's effectiveness; but as of 2012, there was only one anecdotal report of its effective use in patient care, despite hundreds being deployed [13]. A similar clamp targeting the aorta has been proposed to arrest inguinal hemorrhage [14].

In the current study, we evaluate a novel method of hemorrhage control, based on electrical stimulation of blood vessels with microsecond pulses [15], [16]. Though vasoconstriction was long reported in response to direct electric current, it was accompanied by tissue damage [17], [18], probably due to excessive heating or electrochemical reactions caused by the charge imbalance. Charge-balanced pulsed electrical stimulation, on the other hand, can avoid irreversible electrochemical reactions and tissue damage at the electrode–tissue interface [19]. Pulsed electrical stimulation of chicken embryo caused vasoconstriction in 10 s and thrombosis after 3 min [20]. Recent studies using microsecond and millisecond pulses have demonstrated vasoconstriction and reduced bleeding in femoral and mesenteric vessels in rats or in injured liver in rabbits, without tissue damage [15], [16].

In the current paper, we describe an effective, easy-to-use, portable device for hemorrhage control, which should help minimize bleeding until the injured is evacuated to a medical facility [21]. We explore the feasibility of providing sustained vasoconstriction for several hours using a portable, battery operated miniature stimulator.

II. Methods

Based on evaluation of the vasoconstriction thresholds in our previous studies [16] and in current experiments, we elected to design the portable device to operate at 20 V due to the following reasons. First, 20 V provides vasoconstriction sufficient to reduce vessel diameter by a factor of 3, cross-sectional area by a factor of 9. Second, 20 V can be simply and inexpensively supplied using a stack of several 3-V coin batteries, eliminating the need for bulky, power consuming voltage converters. Third, the use of low-voltage components and integrated circuits greatly reduce the device size and cost.

A. Animals

Male, wild-type Long Evans rats, aged 50–60 days, were used for this study (Charles River, Wilmington, MA). The average animal weight was 263 g. Animals were anesthetized with 75 mg/kg Ketamin HCl and 5 mg/kg Xylazine. An additional half dose was given every 45 min, when necessary. Buprenorphine (0.01 mg/kg) and Hartman's Lactated Ringer Solution (114 ml/kg/24 h, 37 °C) were administered subcutaneously at the beginning of the experiment for pain control and hydration. Animal experiments were approved by the Stanford Administrative Panel on Laboratory Animal Care.

B. Surgery

With the animal in the supine position, the internal temperature was monitored and held to 37 ± 1 °C using a heating pad. The femoral artery was exposed by removing the skin and fascia. Hartman's Lactated Ringer solution (37 °C) dripped onto the surgical site throughout surgery and experiments. After exposure, the vessel was allowed to acclimate for 15 min before any experiments were performed.

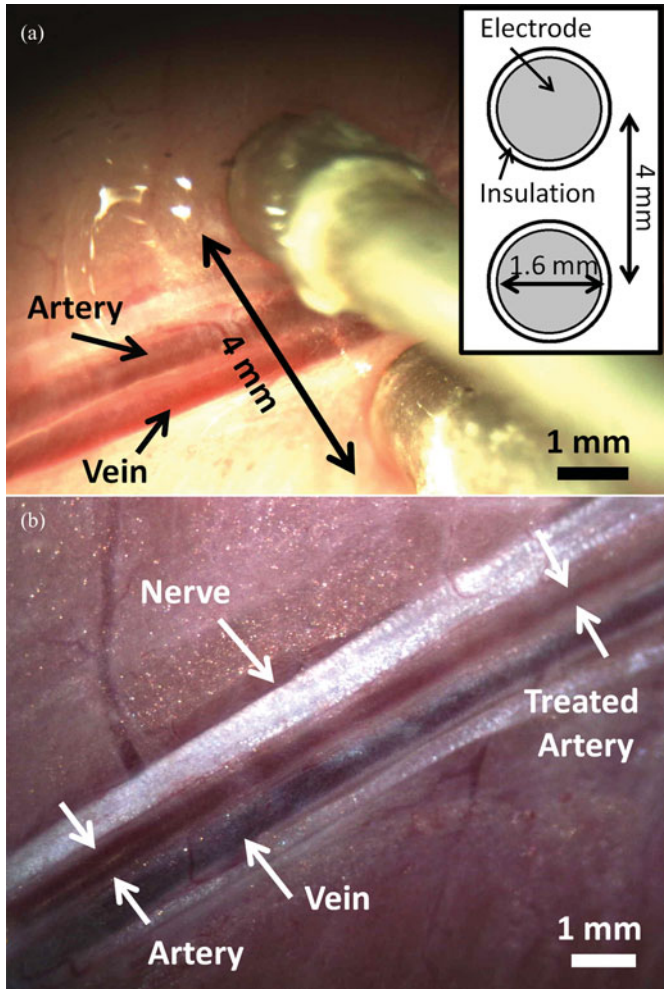

Fig. 1. (a) Two 1.6-mm diameter electrodes, 4 mm separation, were placed across and equidistant from the vessels. Disc electrodes represent the exposed end face of the insulated 1.6-mm diameter (inset). (b) Femoral vessels with arrows indicating the original and the constricted artery widths. The femoral vein (bottom) has a darker lumen than the artery (middle).

C. Vessel Stimulation and Data Collection

Stainless steel wires (3 N8 purity, EPSI Metals, Ashland, OR) were coated with insulating spray, except for the circular end-face, to create 1.6-mm diameter stainless steel disc electrodes. Since the stimulation target is the blood vessels, the two electrodes spaced 4 mm apart were placed with the artery and vein centered between them (see Fig. 1). Monophasic, anodic pulses were generated using a customized pulse generator. A 10-μF capacitor between the generator and one of the electrodes assured charge balance of each pulse cycle. Stimulation waveforms were captured and monitored using an oscilloscope (Tektronix 3034 B, Beaverton, OR). Current was calculated from the voltage drop across a 10-Ω series resistor. The effect of pulse duration on vasoconstriction was studied for 1, 10, and 100 μs, and 1 and 10 ms pulses of 20-V at 10-Hz repetition rate.

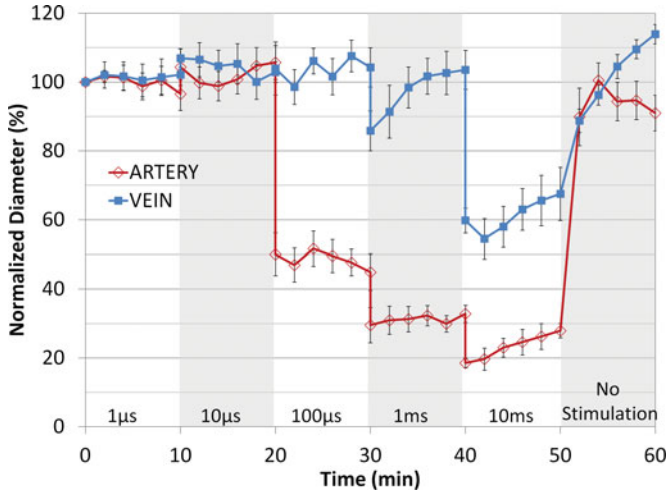

Fig. 2. Normalized vessel diameter during stimulation with various pulse durations. The 20-V amplitude and 10-Hz repetition rate remained constant, while the pulse duration was swept from 1 μs to 10 ms, changing by a factor of 10 every 10 min. Vessel diameter was recorded every 2 min and within 15 s after the change in pulse duration. At 50 min, the stimulation was terminated and the vessel relaxed. Error bars show SEM. The difference between the average arterial constriction obtained with 100-μs and 1-ms pulses was highly significant: $p = 0.01$ ($n = 5$).

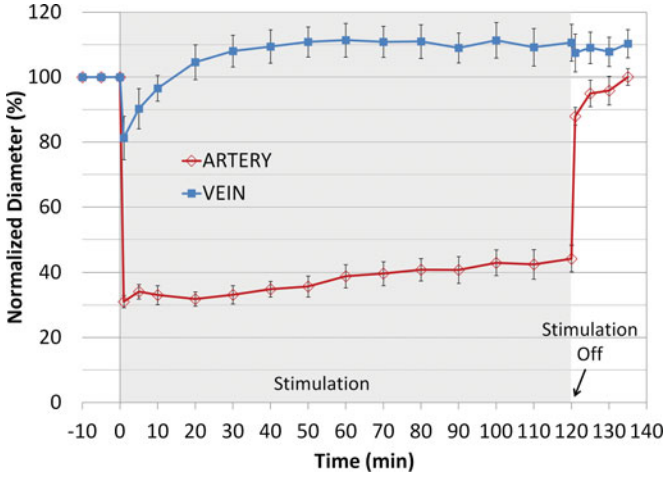

Fig. 3. Femoral artery constricted to 31 $\pm$ 2% to 44 $\pm$ 4% of the initial diameter during 120-min-long stimulation, and dilated to 88 $\pm$ 3% within 1 min after stimulation ($n = 6$). Error bars show SEM.

Sustained electrical stimulation was applied for 120 min using 20-V, 1-ms pulses at 10-Hz repetition rate.

The blood vessel lumen diameters were measured from the images captured with a digital camera (TC202 USB-A, Sentech Inc.) using ImageJ software (NIH, Bethesda, MD). The bleeding rate from the arterial injury was measured using blood collection with preweighed KimWipes. Using the weight change and knowing the blood density (1060 mg/ml), the collected blood volume was calculated. In the bleeding experiments, stimulation was applied with 1-ms pulses at 10-Hz repetition rate using 20- and 100-V amplitude. All results are presented as mean $\pm$ SEM. Statistical significance was determined using the Student's t-test.

D. Histology

After stimulation, the skin and fascia were closed using a 6–0 silk suture. After seven days, the vessel stimulation site was once again exposed and 10% buffered formalin was applied topically for 20 min. After euthanasia, the vessel was dissected and immersed in 10% buffered formalin overnight. The tissue was then dehydrated with a graded series of ethanols, fixed in paraffin, sectioned and stained with hematoxylin and eosin (H&E).

III. Results

A. Effect of Pulse Duration on Vessel Constriction

To explore the effect of pulse duration on vessel constriction, 20-V stimulation pulses were applied for 10 min with pulse durations of 1, 10, and 100 μs, and 1 and 10 ms at a 10-Hz repetition rate. As shown in Fig. 2, no response was observed for 1- and 10-μs durations, but within seconds of applying the 100-μs pulses, the artery constricted to 50 $\pm$ 6% of the original diameter. The artery further constricted to 30 $\pm$ 5% with 1-ms pulses ($p = 0.01$), while the vein only constricted transiently to 86 $\pm$ 6%. The 10-ms pulse duration added only transient improvement to arterial response: after initial constriction to 19 $\pm$ 1%, the artery slowly dilated back to 28 $\pm$ 2%. However, the vein constricted to approximately 60 $\pm$ 4%.

B. Sustained Vasoconstriction

Two important characteristics of a hemorrhage control device are its ability to 1) maintain vasoconstriction and prevent blood loss for a few hours, until the patient is evacuated, and 2) rapidly restore the flow when patient arrives at the definitive treatment center. The 20-V, 10-Hz, 1-ms stimulation was able to sustain the constriction of the femoral artery for two hours, which then rapidly recovered to its original diameter after stimulation ended (see Fig. 3). The artery constricted initially to 31 $\pm$ 2% and then gradually dilated to 44 $\pm$ 4% during the two hours of stimulation. Interestingly, the vein constricted only transiently to 81 $\pm$ 7%, and dilated to 110 $\pm$ 6% of the initial normalized diameter during the first 15 min. After the end of stimulation, the artery recovered to 88 $\pm$ 3% of its diameter within one minute. Vessel histology at 24 h (not shown) and one week after stimulation (see Fig. 4) did not show any obvious damage caused by the prolonged stimulation.

C. Control of Blood Loss in Severe Arterial Injury

To assess the rate of blood loss in severe injury of the femoral artery, it was completely cut and the volume of blood lost during 2 min was recorded with and without electrical stimulation (n = 5 for each group). Fig. 5 shows the bleeding rate (ml/min) averaged over the two-minute collection time. Bleeding rate during 100-V and 20-V stimulation at 10 Hz with 1-ms pulses is compared to a control (no stimulation). The 20 V stimulation reduced the bleeding rate by more than 3.5 fold from 1.04 $\pm$ 0.12 to 0.29 $\pm$ 0.08 ml/min ($p = 0.0075$). The 100-V stimulation reduced the bleeding rate by 9 fold—down to 0.11 $\pm$ 0.04 ml/min ($p < 0.001$).

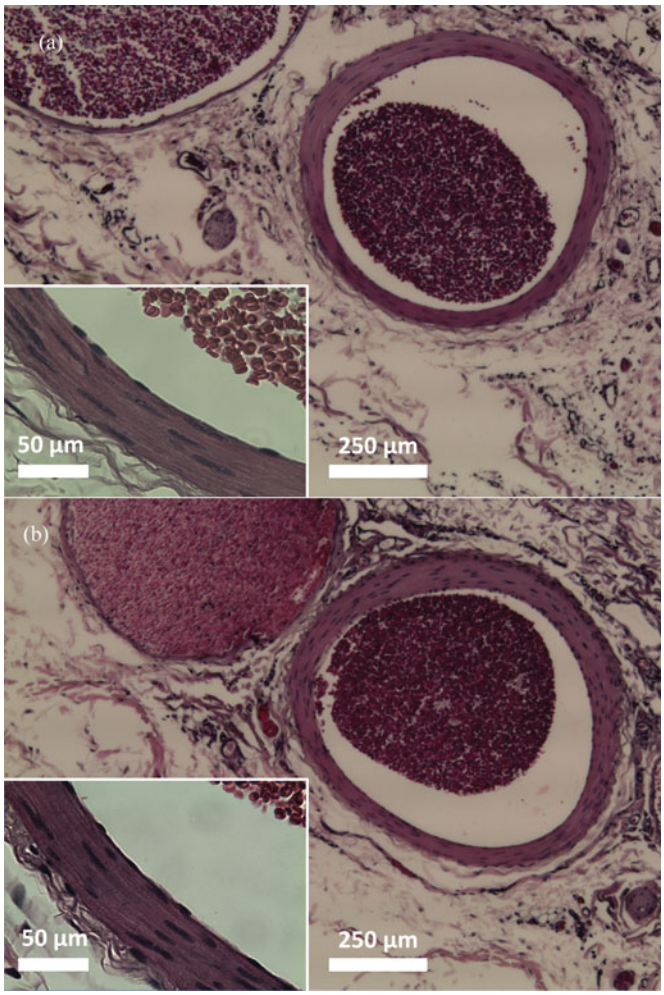

Fig. 4. (a) Histological sections of femoral artery at seven days following a two-hour treatment with 20-V, 1-ms pulses at 10-Hz repetition rate. Inset shows a healthy vessel wall and endothelium. (b) Control vessel and arterial wall (inset). Samples stained with H&E.

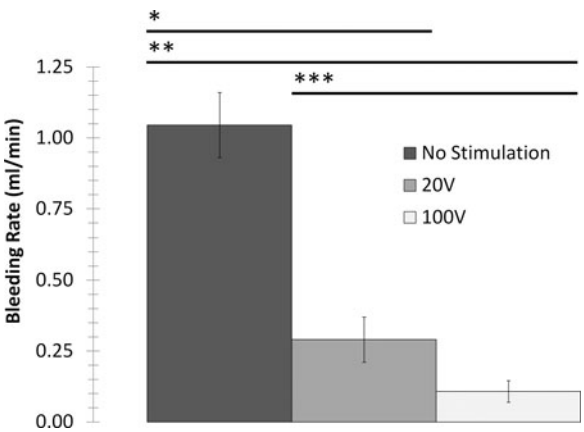

Fig. 5. Bleeding rate following a complete cut of femoral artery. Vessels were stimulated with either 20-V or 100-V, 1-ms pulses at 10-Hz repetition rate. Control vessels were prepared in a similar fashion and the electrodes were placed proximal to the injury, but no stimulation was applied. Error bars show SEM. Statistical differences between groups according to the Student's t-test: $*p = 0.0075$; $**p = 0.00025$; $***p = 0.07$ ($n = 5$).

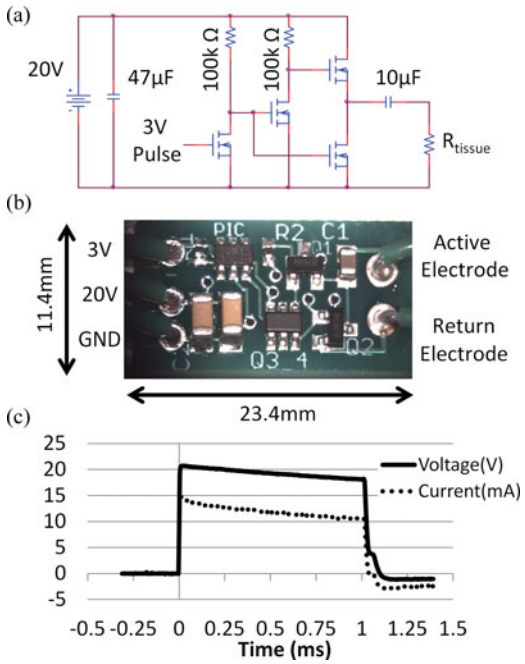

Fig. 6. (a) Miniature stimulator circuit schematic. (b) Stimulator assembled on a PCB of 11 × 23 mm in size. (c) Voltage and current output waveforms of the device with tissue load (average, $n = 4$).

D. Miniature Stimulator for Hemorrhage Control

To use a hemorrhage control device in the field, the apparatus should be small enough to fit into a first aid kit and should allow several hours of battery-powered operation. As a proof of concept of such miniaturization, we designed and fabricated the 11-mm × 23-mm device shown in Fig. 6. The stimulator includes a programmable microcontroller (PIC10 F 202, Microchip), powered with the 3-V supply, which serves as a pulse generator with adjustable duration and repetition rate. The pulse generator employed a NMOS push–pull output stage to deliver the supply voltage (∼20 V) to the 1.6-mm diameter stainless steel disc electrode. Eight, 3-V Lithium Batteries (CR927, Evergreen), stacked together (9.5-mm diameter, 21.6-mm in length), supplied sufficient voltage to generate pulses of 20.7 V. We elected to stimulate with asymmetric charge-balanced pulses to reduce the device size-monophasic pulses requires only one +20 V power supply. As long as the vessel is equidistant from the two electrodes the vasoconstriction effect will be similar to a biphasic pulse and invariant to electrode polarity. To ensure charge balance, the output was coupled to electrodes via 10-μF coupling capacitor. The recharge time constant was more than 13 ms. The rise and fall times (10%–90%) of the voltage waveform were 7 and 62 μs, respectively. An example of a 1-ms pulse generated on a tissue load at 10-Hz repetition rate is shown in Fig. 6(c). The 10-μF coupling capacitor charged to approximately 2.5 V during the pulse, evidenced by the voltage drop from 20.7 to 18.2 V. The falling edge of the pulse is composed of two phases: when the first transistor (push) of the output cascade is turned off, the current drops to zero, and when the second transistor (pull) opens, the current becomes negative, recharging the coupling capacitor. During the idle phase, the device

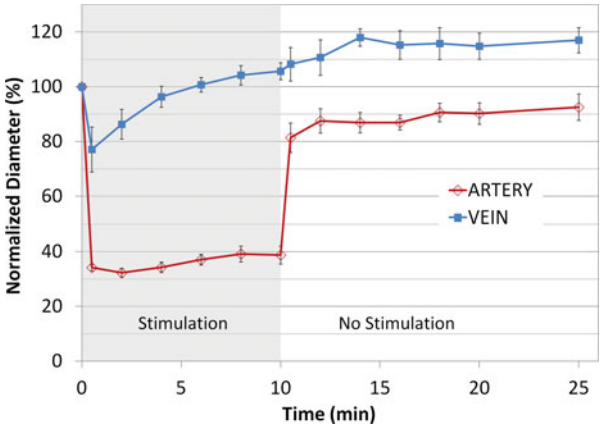

Fig. 7. Vessel constriction using miniature stimulator. The artery constricted to 34 ± 1%, similar to the response obtained with the bench-top pulse generator (see Fig. 1 and Fig. 2). The vein constricted only transiently. Error bars show SEM.

operated with 0.45 mA, while during the pulse, the maximum current draw was 15 mA. To stabilize the supply voltage and effectively draw current from the battery, a 44-μF capacitor was connected parallel to the battery pack, which drew an average current of 0.6 mA from the batteries. With a battery capacity of 30 mAh, even 10% use of its storage capacity should suffice for 5 h of operation.

Effectiveness of the mini-stimulator was also tested on femoral vessels for 10 min (see Fig. 7). The normalized artery diameter constricted to 34 ± 1%, similar to the same treatment obtained with the bench-top stimulator (see Figs. 1 and 2).

IV. Discussion

The 20-V, 10-Hz, 1-ms stimulation applied via a bipolar pair of 1.6-mm electrodes resulted in rapid (within seconds) constriction of the rat femoral artery to 31 ± 2% of its diameter, which was maintained throughout a 2-h period, albeit with slow relaxation to 44 ± 4% by the end of the treatment. Surprisingly, the bleeding rate decreased only by 3.5 fold at these setting, compared to control. One could expect the flow rate decrease at least as a square of the vessel diameter. However, the control vessel also constricts in response to dissection and bleeding. In addition, the reduced blood pressure and extra-luminal clotting [22]–[24], both intrinsic hemostatic response mechanisms, may further reduce the bleeding rate in the control group. Therefore, the advantage of electronic vasoconstriction over no treatment is likely affected by the extent of natural hemostatic ability of the ruptured vessel. An alternative mechanism of the reduction in blood loss was suggested to be caused by blood clotting due to endothelial cells electroporation [15], [25]. However, it is unlikely to play a role in the current study, given the lack of the endothelial cell damage upon histological examination.

The mechanism of vasoconstriction in response to electrical stimulation involves activation of sympathetic nerve fibers embedded in the vessel wall and the release of noradrenaline, which binds to the α_1-adrenoreceptor [26]–[30]. Stimulation of the rat mesenteric artery with 5-ms pulses of 15–30 V at 10–50 Hz, applied via bipolar electrodes, was shown to induce vasoconstriction solely by engaging the sympathetic fibers [28]. Similar to our results, they noted rapid dilation within a few seconds of the treatment termination and slight relaxation of the constricted vessel after 30 min of sustained stimulation. Importantly, rapid dilation of the vessel restores the blood flow once a patient is stabilized, which should help prevent unnecessary ischemia and associated tissue damage during definitive surgery. Possible direct engagement of the smooth muscle cells of the vessels' walls at higher voltage stimulation requires further investigation.

Despite a significant vasoconstriction of the arteries in response to 20-V, 1-ms waveforms, the veins responded weaker at these settings and would likely require stronger stimuli. Previous studies indicate that strong vein constriction occurs at higher voltage (60 V with 1 ms) [16], [31] or longer pulse durations (20 V with 10 ms in the current study). At low voltage, veins exhibit short constriction and slow dilatory response, observed in our study and in previous experiments with rabbit portal vein (15-V, 1-ms pulses at 10 Hz) [32]. Vein relaxation has been linked to the release of nonadrenergic noncholinergic neurotransmitters, such as nitric oxide and ATP [32], [33]. Despite weak venous response, constricted arteries will minimize blood loss through damaged veins indirectly. If needed, higher voltage or longer pulse durations can be used to achieve significant vein constriction [16].

Importantly, electrical stimulation provided sustained arterial constriction for two hours with no apparent damage to vessel walls or endothelium, thus leaving the tissues well-preserved for the following surgery and therapy.

Severe loss of blood, defined as more than 40% of total blood volume, corresponding to the advanced trauma life support (ATLS) shock class IV, is associated with mean mortality of 26%. A three-fold lower volume, i.e., loss of less than 15% (ATLS class I shock), is associated with less than 4% mortality [34]. Though it might be difficult to directly extrapolate the significance of our results to clinical setting, a 3.5 fold decrease in bleeding volume might save many lives.

Stimulation parameters for effective control of bleeding in trauma care will require further investigation in larger animal models and, eventually, in human patients. Practical application of electrical stimulation in large wounds with poor visibility of the vessels will likely require an array of penetrating electrodes integrated with microsensors. Detection of the temperature, conductivity, and hemoglobin oxygenation ratio will help localize the source of bleeding and activate the electrodes proximal to that location. Alternatively, implantable microstimulators could be injected into the bleeding tissue and powered wirelessly to induce local vasoconstriction [35]. Since wireless power transmission is rather inefficient, the transmitter will likely be bulky and require a large power supply. In addition, lack of visibility inside the wound will still require multiple electrodes and sensors to activate the ones proximal to the bleeding site.

V. Conclusion

Pulsed electrical stimulation of the vasculature by a miniature battery-operated generator can constrict the femoral artery

in rats within seconds, sustain constriction for multiple hours, and then release the vessel within a minute after termination of the stimulation. Extent of constriction can be controlled by pulse amplitude, duration and repetition rate. The blood loss from injured femoral arteries in rats can be reduced by more than three-fold with 20-V pulses, and more than nine times with pulses of 100 V. Further experiments in larger animals are required to optimize the stimulation protocol and evaluate the potential of this technology for human use.

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Mark R. Brinton (S'13) received the B.S. and M.S. degrees in electrical engineering from the University of Utah, Salt Lake City, UT, USA, in 2010. He is currently working toward the Ph.D. degree in electrical engineering from Stanford University, Stanford, CA, USA.

During his M.S., he modeled and studied ultrasonic thermal therapy to induce selective cell death. His current research interests include electrical stimulation of peripheral nerves and muscles, specifically for vasoconstriction and gland secretion. He is a National Defense Science and Engineering Graduate Fellow.

Yossi Mandel received the M.D. degree from the Hebrew University of Jerusalem, Jerusalem, Israel, in 1992, and he is a board-certified Ophthalmic Surgeon. He received the Ph.D. degree in bioengineering from the Hebrew University of Jerusalem in 2011. During his Ph.D. research he studied irreversible electroporation and its application to uveal melanoma treatment. From 2012 to 2013 he was a Postdoctoral Fellow in the laboratory of Dr. Palanker at Stanford University, Stanford, CA, USA.

He is currently an Assistant Professor in the Faculty of Life Sciences, Bar Ilan University, Ramat Gan, Israel. His research interests include brain plasticity and training in artificial vision; restoration of sight with neuronal stem cells; electrical stimulation of the sympathetic nervous system, and various microfluidic applications in ophthalmology.

Roopa Dalal, photograph and biography not available at the time of publication.

Daniel Palanker received the Ph.D. degree in applied physics from the Hebrew University of Jerusalem, Jerusalem, Israel, in 1994.

He is currently an Associate Professor in the Department of Ophthalmology and in the Hansen Experimental Physics Laboratory at Stanford University, Stanford, CA, USA. His research interests include interactions of electric field with biological cells and tissues in a broad range of frequencies: from quasi-static to optical, and develops their diagnostic, therapeutic, and prosthetic applications, primarily in ophthalmology. Several of his developments are in clinical practice world-wide: Pulsed Electron Avalanche Knife (PEAK PlasmaBlade$^{\mathrm{TM}}$), Patterned Scanning Laser Photocoagulator (PASCAL$^{\mathrm{TM}}$), and OCT-guided Laser System for Cataract Surgery (Catalys$^{\mathrm{TM}}$). In addition to laser-tissue interactions, retinal phototherapy, and associated neural plasticity, he is working on electro-neural interfaces, including retinal prosthesis, and electronic control of vasculature and of the glands.