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Versatile electrical stimulator for providing cardiac-like electrical impulses *in vitro*

Stefano Gabetti,^{1,2} Giovanni Putame,^{1,2}
Federica Montrone,^{1,2} Giuseppe Isu,³
Anna Marsano,³ Alberto Audenino,^{1,2}
Diana Massai^{1,2}

¹Polito^{BIO}Med Lab, Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy;

²Interuniversity Center for the Promotion of the 3Rs Principles in Teaching and Research, Italy;

³Department of Surgery and Department of Biomedicine, Basel University Hospital, Basel, Switzerland

Abstract

In the perspective of reliable methods alternative to *in vivo* animal testing for cardiac tissue engineering (CTE) research, the versatile electrical stimulator ELETTRA has been developed. ELETTRA delivers controlled and stable cardiac-like electrical impulses, and it can be coupled to already existing bioreactors for providing *in vitro* combined biomimetic culture conditions. Designed to be cost-effective and easy to use, this device could contribute to the reduction and replacement of *in vivo* animal experiments in CTE.

Introduction

Cardiac tissue engineering (CTE) aims to develop functional substitutes of native myocardium to be exploited as *in vitro* models for cardiac development and disease research, and ultimately for cardiac repair.¹ In the perspective of reliable methods alternative to *in vivo* animal tests,² bioreactors are technological devices designed to provide biomimetic culture environments *in vitro*. In CTE they are widely used as model systems to investigate the individual or combined effects of cardiac-like physico-chemical stimuli on cardiac cells and substitutes, with the advantage of excluding systemic effects existing *in vivo*.³ Here we present the versatile electrical stimulator ELETTRA, designed to provide controlled cardiac-like electrical impulses for CTE applications and to be integrated in already existing bioreactors.

Materials and Methods

ELETTRA design was guided by specific requirements: accuracy in mimicking the *in vivo* pulsatile electric field experienced by human cardiac cells (resting rate = 1.0-1.7 Hz, electric field = 0.1-10.0 V/cm, pulse duration = 1-2 ms);³ versatility to be used with different bioreactors; ease of use; cost-effectiveness. ELETTRA's core consists of an Arduino Due board running a purpose-built software, interfaced to analog and digital peripherals. A user-friendly interface, based on a push button, a rotary

Correspondence: Polito^{BIO}Med Lab, Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Turin, Italy.

E-mail diana.massai@polito.it

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encoder and an LCD display, allows the tuning of stimulation parameters. Banana sockets are used as output ports and a sensing resistor enables monitoring the current flowing between the electrodes. Control and stimulation subunits allow to separately increase stimulation amplitude and deliver monophasic or biphasic pulses in a wide range (frequency = 0.5-10.0 Hz, amplitude = 0.5-12.0 V, pulse duration = 1-10 ms). To test the system, ELETTRA was connected to two carbon rod electrodes (length = 2.5 cm, diameter = 0.3 mm) embedded in a sil-

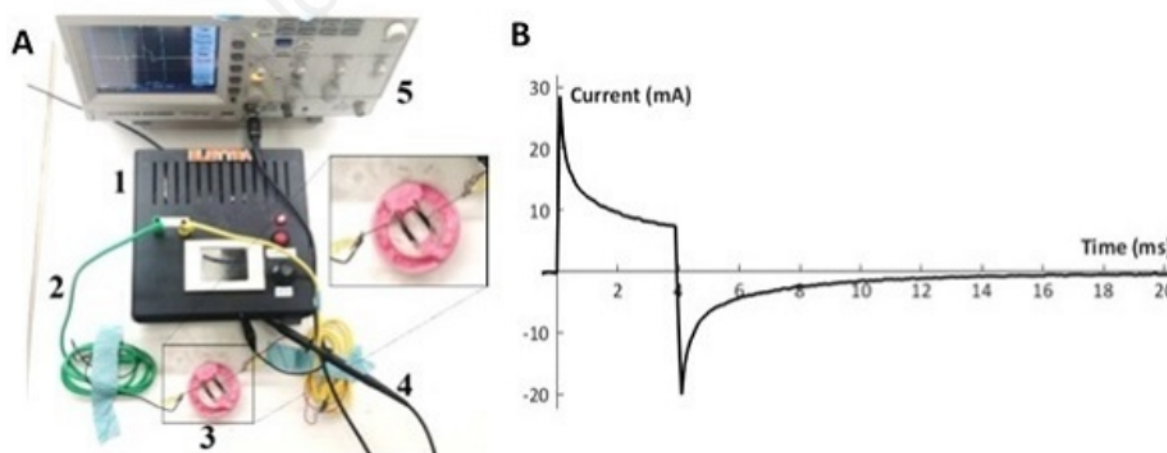


Figure 1. A) Experimental testing setup: 1. ELETTRA; 2. Connectors; 3. Electrode-holder assembly in Petri dish; 4. Sensing circuit probe; 5. Oscilloscope. Inset image: Electrode-holder assembly. B) Plot of the average current vs time for monophasic stimulation (5 V, 1 Hz, 4 ms) as measured by the sensing circuit.

icone holder at a fixed distance of 1 cm, and placed in a Petri dish with saline solution (Figure 1A). Monophasic square waves (1 Hz, 4 ms) with four different amplitudes (5.0, 7.5, 10.0, 12.0 V) were imposed. A digital oscilloscope was used to measure the total voltage and the voltage drop on the sensing resistor. For each condition, 20 subsequent pulses were recorded. Data were processed to calculate the maximum flowing current and the time constant.

Results

Preliminary tests on ELETTRA confirmed satisfactory stimulation performances, ease of use and cost-effectiveness, with an overall cost below € 100. Voltage amplitude resulted stable during stimulation. As regards the average current between the electrodes (Figure 1B), it increased instantly as the electrical stimulation was provided with a following decrease

due to the induced polarization of the solution. During passive phase, the accumulated charges were released in the solution and the current reversed its direction. The maximum current flowing between the electrodes varied from 29 to 79 mA, depending on the imposed voltage. For each condition, the calculated time constant was always lower than 1 ms.

Conclusions

ELETTRA delivers a controlled and stable stimulation mimicking the cardiac electrical impulses. This device could significantly contribute to the reduction and replacement of *in vivo* animal experiments for investigation of cardiac development and disease and for preclinical validation of engineered cardiac constructs. Biological tests are ongoing on cardiomyocyte monolayers to investigate the impact of electrical stimulation on cell maturation.

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