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REVIEW ARTICLE

Isolated heart models: cardiovascular system studies and technological advances

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Abstract Isolated heart model is a relevant tool for cardiovascular system studies. It represents a highly reproducible model for studying broad spectrum of biochemical, physiological, morphological, and pharmaceutical parameters, including analysis of intrinsic heart mechanics, metabolism, and coronary vascular response. Results obtained in this model are under no influence of other organ systems, plasma concentration of hormones or ions and influence of autonomic nervous system. The review describes various isolated heart models, the modes of heart perfusion, and advantages and limitations of various experimental setups. It reports the improvements of perfusion setup according to Langendorff introduced by the authors.

Keywords Isolated heart · Langendorff · Neely · Monophasic action potential · Electrogram

1 Introduction

The isolated perfused hearts remain relevant models in cardiovascular system studies for over a century. They represent feasible, highly reproducible and greatly comparable models for studying a broad spectrum of physiological, morphological, biochemical, and pharmacological parameters. The models of isolated heart also recently found application as a valuable approach for scoring cardiotoxicity and pro-arrhythmic potential of various drugs in the field of molecular biology and biomedical engineering.

Since the introduction of the isolated frog heart model, numerous improvements and modifications have been realized. In this review, progress of isolated mammalian heart models and their applications are presented.

2 History

The first experiment with artificially perfused heart was performed by Wild and Ludwig already in 1846. In this experimental setup, the heart of the killed animal was connected to the carotid artery of a living donor animal, which maintained perfusion of the coronary arteries of the recipient heart [62]. The first completely excised and artificially perfused heart was reported by Ludwig and Cyon two decades later, in 1866. They used a much simpler model without coronary arteries: the frog heart nourished only by diffusion [8]. Despite the obvious differences between the amphibian and mammalian hearts, the isolated frog heart model helped to elucidate many important principles of cardiovascular functioning, such as the role of calcium ions in cardiac contraction, the "all or none law," absolute refractory period, the origin of cardiac automaticity, and many others [62].

The first mammalian heart preparation was accomplished by Martin [34]. He used artificially ventilated cat and dog with excluded systemic circulation. The blood ejected by left ventricle entered the coronary arteries. In principle, it was the original heart–lung preparation.

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The first completely isolated mammalian heart model was finally achieved by Langendorff [30]. He excised the animal hearts and kept them vital for several hours. His model was based on retrograde delivery of defibrinated blood into the aorta and subsequently into the coronary arteries, due to the closed aortic valve [30].

Although Langendorff isolated heart model has been going through many modifications so far, it proved its simplicity and practicability in cardiovascular research. However, it must be taken into consideration that this model is a retrograde non-working system, which is not able fully to simulate in vivo conditions, and therefore—in some cases—the working mode of isolated heart is more appropriate. Such a model was developed by Neely and Morgan [36]. They converted the Langendorff heart model into the working mode which is closer to the real physiological situation: the heart is perfused ortogradely, and the left ventricle performs the pressure–volume work [36]. Another model for "more physiological" simulations of in vivo conditions was developed by Chinchoy [5] as a four-chamber isolated heart model. Although the four-chamber perfusion may appear even "more physiological" then the working heart according to Neely, this model seems to be more useful only in some specialized fields, e.g., in studying the conductive system or in the experiments focused on right and left heart dysfunction relationship. Another great disadvantage of this model is its high cost and rather difficult preparation and performing the experiment.

3 Advantages and limitations of isolated heart model

The isolated perfused heart models allow the assessment of numerous biological parameters without the influence of humoral and neural regulations. Another advantage of a simple isolated organ model is the possibility to repeat the experiments with high level of reproducibility and comparability of the measured data. The simple isolated organ model also permits to study various conditions and disorders which would be simulated, induced or monitored in vivo with more difficulty. Externally stimulated isolated heart model represents valuable tool for studying localization of the ectopic focuses of electrical activity and elucidation of conditions for arrhythmia triggering [6, 60]. The possibility to record the electrical signal directly from heart surface without interference of other tissues that are known to affect signal transduction also needs to be mentioned.

Since the isolated heart models require killing the animals, it is necessary to respect strict regulations in planning the experiments and adjust the experimental protocol or to select an alternative method. At first, adequate manipulation with the animal prevents stress and undesirable impact of sympatho-adrenergic activation on the experimental results. Similarly, preparation of the heart must be quick, in order to avoid ischemic injury and ATP depletion in the tissue. ATP content in the heart muscle dramatically decreases after 10–30 s of asphyxia [11]. The excessive ATP depletion may lead to incomplete recovery of the electrical and mechanical properties of the isolated heart after cannulation. The preparation thus needs to be quick to avoid cardiac injury due to ischemia, yet gentle enough to prevent mechanical damage of the tissue. Pulling of the heart may lead to damage of the aorta or sinoatrial node, and excessive press during preparation might damage the cardiac tissue. Careful and precise maintenance of optimal experimental conditions (oxygen and nutrient delivery, temperature, and perfusion pressure) must be ensured during the whole experiment in order to obtain exact and reproducible results [50, 51]. Moreover, it has been kept in mind that usage of protein-free solutions in long-term experiments leads to decay of contractile and chronotropic function of the heart due to developing tissue edema [35, 59].

An alternative approach to study the cardiovascular functions without using the experimental animals is possible. Mathematical and electromechanical modeling of the heart function [21, 48] as well as correlation between circulatory networks under simulated conditions have become popular recently [9, 15]. Though such models are useful tools in cardiovascular research, they cannot replace the whole-organ studies completely, due to the limited possibility to model some mechanisms that modify cardiac cycle (e.g., Starling's law) [15].

4 Langendorff isolated heart preparation

The direction of perfusate in this model is retrograde, i.e., opposite as compared to in vivo situation. In an anesthetized animal, the heart is quickly excised and immersed in cold perfusion solution to prevent warm ischemic injury. In our experience with rat hearts, the time of warm ischemia may be shorter than 30 s. Subsequently, it is necessary to restore the coronary flow in order to prevent further ischemic injury of the organ. Therefore, the heart is mounted to cannula and fixed to the perfusion set as quickly as possible. Prior to cannulation, it is necessary to check the cannula and tubes connecting it with the perfusate reservoir to ensure that both are filled and free of air bubbles since the air embolism would terminate the experiment. Special attention must be paid to the prevention of occlusion of coronary ostia by cannula or aortic valve damage during the cannula insertion. Some investigators let the perfusion solution gently dropping from the aortic cannula prior to cannulation in order to minimize the chance of air embolization during heart attachment to the cannula [11,

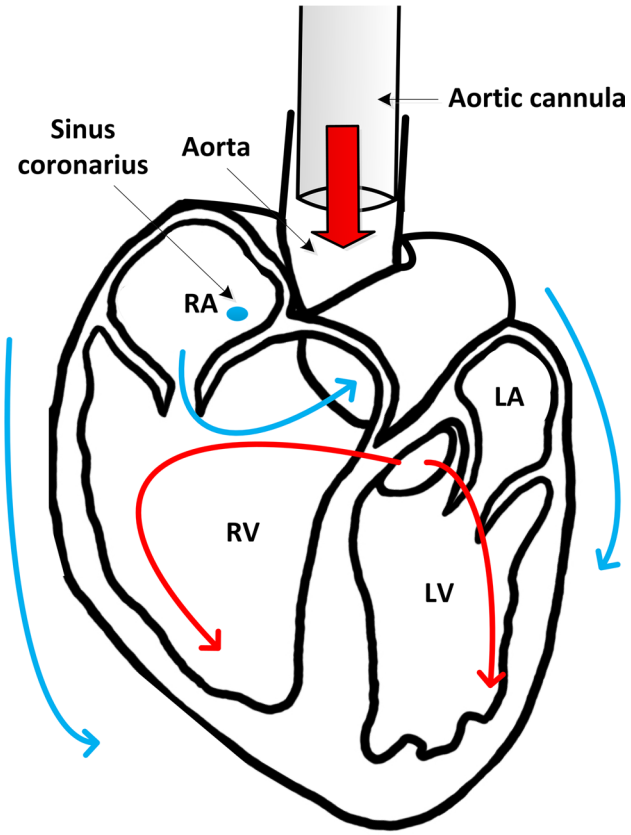

Fig. 1 Isolated heart model according to Langendorff. Perfusion fluid enters aorta through inserted cannula and closes the aortic valves. The fluid then flows into the coronary system, the coronary sinus, and right atrium. The fluid eventually leaves the heart through both venae cavae, right ventricle, and pulmonary vein (marked here as *blue arrows*). *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle (color figure online)

52]. The heart is then fixed by ligature to the cannula, and full flow of the perfusion solution is initiated immediately. Thus, the aortic valves are forcedly closed, and the perfusate is directed into the coronary ostia, draining into the right atrium via the coronary sinus, and leaving the heart (Fig. 1). After the beginning of the perfusion, regular heart rhythm is restored within a few seconds. However, more than 10 min may pass before the heart function is fully stabilized [50]. Therefore, the experiment should be preceded by at least 20 min of stabilization [3].

The experimental conditions need to be precisely set up before and then maintained during the whole experiment. The heart either beats spontaneously or can be paced at a required frequency [56]. The heart can be perfused either by the blood or by carbonate buffers, such as Krebs–Henseleit, Locke, Tyrode, or their variations using HEPES or MES buffers [50]. Most experimenters prefer buffer solution(s) because the usage of blood can lead to undesirable activation of the coagulating system inside the plastic tubes and subsequent infarction of the heart. Also, an inadequate immune reaction may result if the blood of another animal species is used [41, 59]. Proper oxygenation of buffer solution is usually ensured by bubbling with 95 % oxygen. The 5 % carbon dioxide is required to achieve the desired pH (i.e., 7.40), and heater is needed to keep stable temperature of 37 °C [11]. The exact proportional composition of buffer differs among laboratories (especially glucose and calcium concentrations [3, 50]), but it must be considered that hemoglobin and protein-free solutions have poor ability to transport oxygen and lead to tissue edema due to low oncotic pressure [17]. Oxygen transport from the solution to the tissue may be considerably improved by the suspension of perfluorochemicals [27]. Nearly normal osmolality and oncotic pressure are achieved by adding dextran/albumin or mannitol [17, 59]. Other variations of Krebs–Henseleit perfusion solution have also been reported, containing specific substances—pyruvate, fatty acids, or insulin [2, 16, 40].

5 Modifications of Langendorff isolated heart model and their applications

The Langendorff isolated heart model exists in two standard modes depending on perfusate flow into aorta, i.e., constant pressure mode and constant flow mode.

Constant pressure mode is the original Langendorff setup. The value of the perfusion pressure can be easily achieved by adjustment of the reservoir with solution at the demanded height. Due to its simplicity, this system is mostly preferred at present. However, if amount of perfusion solution is limited (e.g., perfusion with enzymes or blood), the constant flow mode is a better choice. The perfusion fluid is then administered by a peristaltic pump. The pump speed needs to be carefully controlled since a too high speed may damage the heart tissue.

For some specific applications, for instance the isolation of cardiac cells, the combination of both modes may be used. Generally, harvesting of viable cardiac myocytes from the whole heart consists of three steps [13, 32]. First step serves for the stabilization of isolated heart and assessment of its quality using common perfusion solution containing calcium (Tyrode, Krebs–Henseleit, etc.). After stabilization, the perfusion solution is changed to calcium-low or calcium-free solution, which disrupts the intercellular connections [32]. These two steps can be done at constant pressure. However, the last part, digestion of the heart tissue with proteolytic enzymes, is better to perform at constant flow since enzymatic digestion impairs the normal vascular function. Impaired coronary flow may lead to inhomogeneous distribution of enzymes and subsequent uneven digestion of the heart tissue. The combined

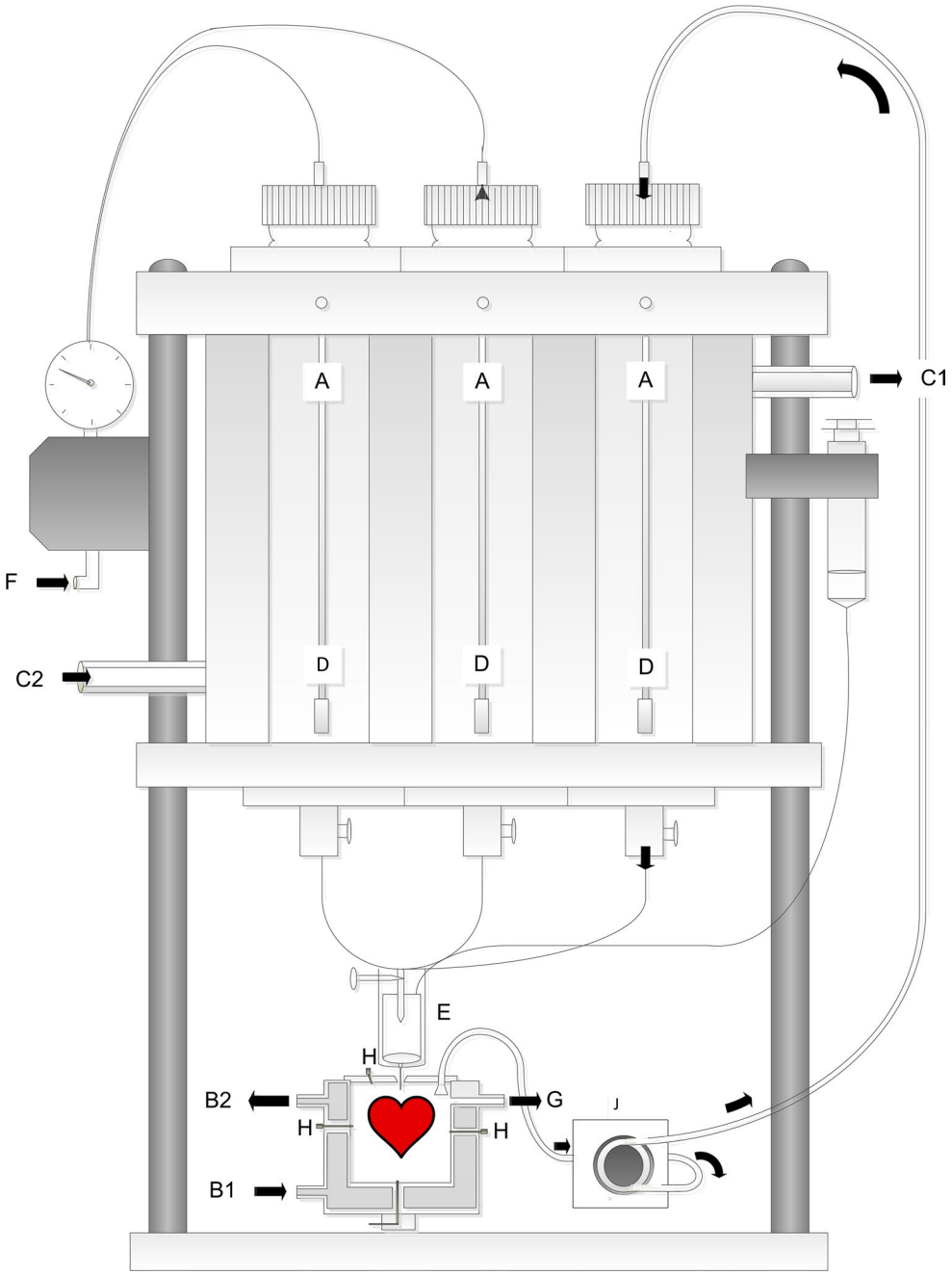

Fig. 2 Modified Langendorff apparatus for isolation of the cardiomyocytes. *A*—reservoirs; *B1*, *B2*, *C1*, *C2*—connection to thermostat; *D*—bubbling stones; *E*—bubble trapper; *F*—pressure-keeping system; *G*—overflow; *H*—electrodes for touchless electrogram recording

apparatus enabling swift switching between two perfusion modes was developed for effective cardiomyocyte isolation in our laboratory. The system develops our previous modification of perfusion apparatus for pharmacological studies [37]. The combined system consists of three columns (50 ml of volume, each oxygenated separately) which are placed in a common warm bath. This makes it possible to maintain constant perfusion pressure despite different amounts of solutions in each column. The first two columns are used for perfusion at constant perfusion pressure. The last column is separated from the pressure-keeping system and is connected to peristaltic pump (Fig. 2). This enables the re-circulation of enzymatic solution during the last step of cardiomyocyte isolation.

6 Isolated working heart preparation

Modification of the isolated heart model with orthograde perfusion and pressure–volume work of the left ventricle was introduced by Neely [36]. The preparation of the heart is the same as in Langendorff isolated heart model—the

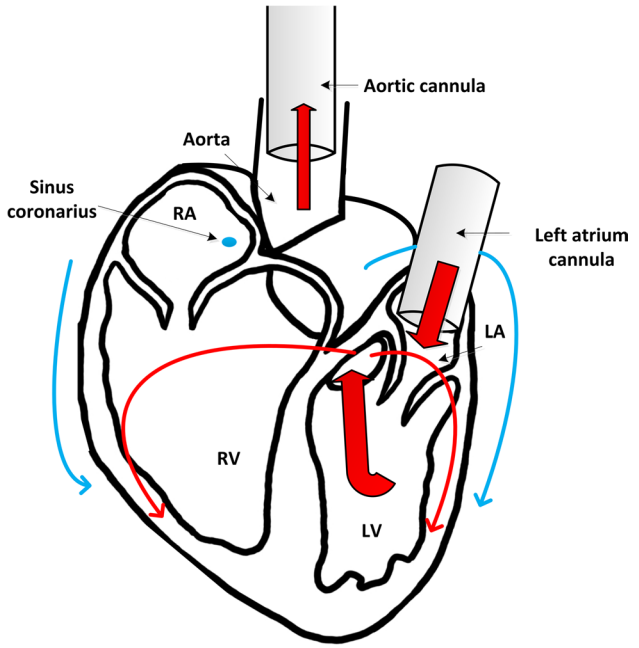

Fig. 3 Isolated working heart model according to Neely. Direction of perfusion fluid mimics the blood flow in vivo. Perfusion fluid enters left atrium via left atrial cannula and continues through mitral valve to left ventricle. The contraction of the left ventricle ejects the fluid into the aorta. Some portion of ejected fluid flows retrogradely to the coronary arteries in diastolic phase of cardiac cycle. The fluid is drained from coronary arteries to coronary sinus and through vena cava, right ventricle, and pulmonary vein leaves the heart (marked here as *blue arrows*). *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle (color figure online)

heart is excised, mounted to aortic cannula, and stabilized for approximately 20 min. Next, the second cannula is inserted to the left atrium via ostium of the pulmonary veins or through artificial opening in the auricle of the left atrium. The perfusion solution flow is then switched to left atrium, continues through the mitral valve to the left ventricle, and during its contraction is ejected to the aorta. A certain portion of the ejected fluid flows to the coronary arteries during the diastolic phase of the cardiac cycle and supplies the heart by nutrients. The perfusion fluid is then drained to coronary sinus and leaves the heart. To mimic vascular elasticity, a compliance bubble trap containing an air bubble is added to the perfusion circuit.

As mentioned above, the working heart apparatus contains two cannulas—one in the aorta and the second in the left atrium (Fig. 3). The key parameter of both cannulas is their adequate size defined by inner diameter—it has to be sufficiently large in order to dispatch the total cardiac output. Cardiac output under in vivo conditions equals the venous return from the lungs to the left atrium. In isolated working heart, the venous return is represented by the flow through the left atrial cannula. Thus, the left atrial perfusion

Table 1 Inner diameter of cannulas for commonly used laboratory animal species

Animal species	Diameter of aortic cannula (mm)	Diameter of atrial cannula (mm)
Mouse	1.0	1.3
Rat	2.0–3.0	2.3–2.5
Guinea pig	2.5–3.0	2.3–2.5
Rabbit	3.0–5.0	3.0–6.0

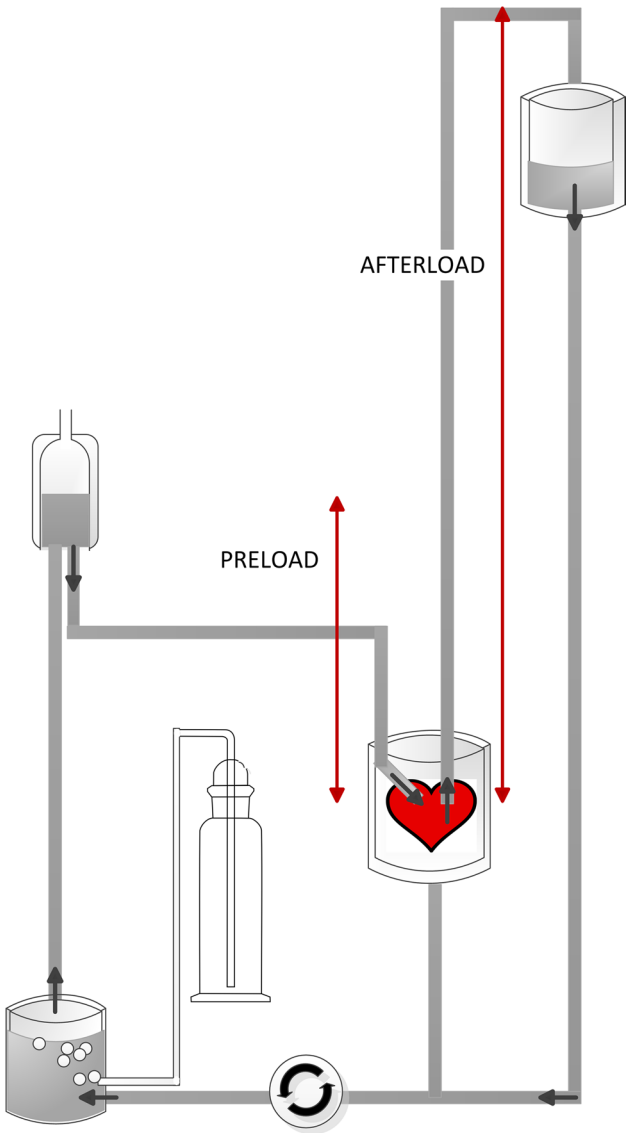

Fig. 4 Working isolated heart setup. The preload is determined by the height of the atrial reservoir from the heart. The afterload is determined by the vertical distance (height) of reservoir from the aortic cannula or by aortic resistor

system must be capable of delivering perfusion fluid at a rate sufficient to support the maximum cardiac output of a working heart at any particular preload. If the left atrial

cannula is too small, it may artificially limit the cardiac output. The adequate size of both cannulas needs to be chosen for each animal with respect to species and strain. Also, age and individual size of the heart must be considered. Commercially available size (inner diameter) of aortic and atrial cannulas for commonly used experimental animals is summarized in Table 1. In our laboratory, we have good experience with following inner diameter of cannulas: 2.0 mm for rat, 2.0–2.5 mm for guinea pig, and 3.0 mm for rabbit heart (adult animals). Other two parameters which must be correctly set up are the pressure under which the perfusion fluid enters the left atrium (preload) and the pressure against which the left ventricle ejects it (afterload), respectively. Preload of the working heart model is determined by the height of the overflow from the atrial perfusion bubble trapper above the heart. Afterload is determined by the height of the reservoir above the aortic cannula (Fig. 4).

7 Animal species used for isolated heart models

First, amphibian hearts were used for the isolated perfusion due to simplicity. At present, virtually all experimental animals used for isolated heart model are mammals. The proper species must be selected taking into account all the specific requirements of each experiment. Use of large animal's heart (pig, monkey, dog, sheep, or even calf) has certain specific advantages: the obtained results show better approximation to human hemodynamic characteristics [22, 33], and mapping of conduction pathways is quite easy due to the heart size [4, 22]. The main disadvantages of large animals are relatively high cost (including breeding and keeping the animals) and immense consumption of the perfusion solution. Rodents (rat, mouse, rabbit, hamster, guinea pig) are preferred due to low price, keeping and breeding costs, and easy manipulation. Small animals are employed in such experiments where high degree of similarity with the human heart is not requested or in extensive drug-testing studies [22]. Mouse became popular in experimental cardiology due to the newly developed methods of genetic manipulation. Possibility of deletion or up-regulation of specific genes enables better understanding of their impact on physiological processes and their involvement in the pathophysiology of various disorders [39, 53]. It also allows simulation of various genetic disorders. The application of murine heart in isolated working heart system is challenging due to its small size. Nevertheless, in 1993, Grupp et al. [20] successfully examined functional parameters in isolated, working mouse heart.

8 Recording methods on isolated heart models

8.1 Electrogram

The electrogram (EG) is a record of the electrical activity from the heart surface. It allows detection of the abnormalities of cardiac rhythm, changes of morphology of the EG curve, or duration of each EG segments. Among other applications, it may be used for instance for assessment of pro- and antiarrhythmic potential of various drugs [58]. The EG recording methods have been improved gradually. The first approaches based on electrodes touching the heart surface were displaced by touchless recoding system, originally reported by Uematsu et al. [57] and later used in improved perfusion apparatus by Novakova [37]. Employment of the touchless electrodes helps to record multiple leads from different parts of the heart without damaging the

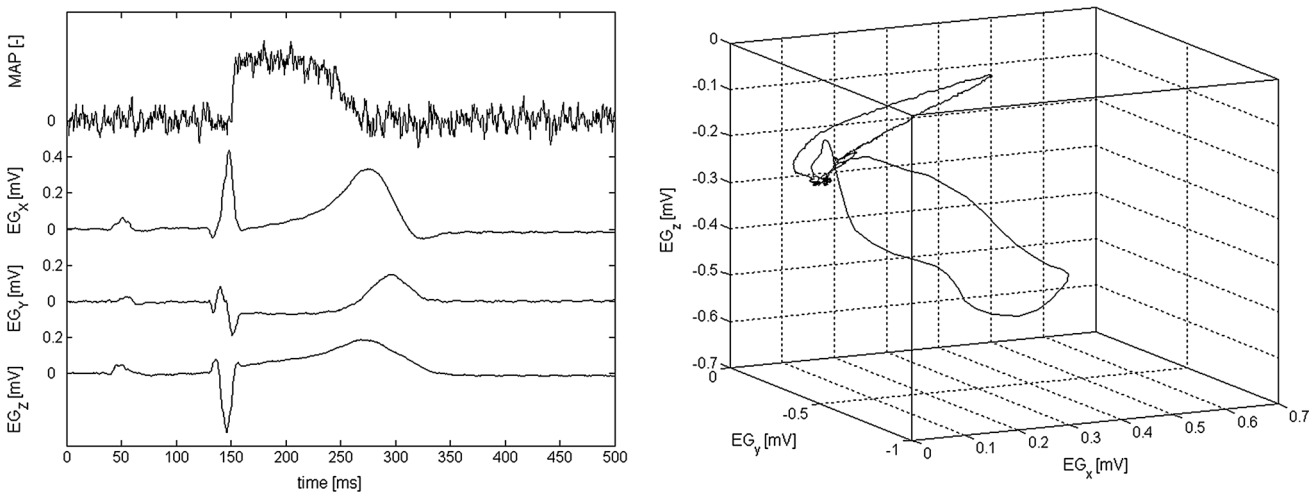

Fig. 5 Original record of monophasic action potential (*upper left*), corresponding electrograms recorded from orthogonal bipolar leads—X, Y, and Z axis (*bottom left*) and corresponding vectocardiogram (*right*)

tissue. Six silver–silver chloride disk electrodes (4 mm in diameter) are placed on the inner surface of the bath and its cover, embedding the heart [44]. The bath is filled with perfusion (i.e., conductive) solution, and thus electrical recording is possible. The six electrodes are positioned as to confirm three orthogonal bipolar leads (X, Y, and Z). The signals recorded from these leads are amplified by bioamplifiers and digitized at a sampling rate of 1000–4000 Hz (based on application) by a three-channel, 16-bit AD converter. The signals are acquired by a LabVIEW compatible data acquisition multifunction card PCI-6250 (National Instruments, USA). The maximum amplitude of recorded signals varies between 100 and 500 μV, depending on the subject (rabbit, guinea pig, and rat). The EG recorded in this way resembles clinical electrocardiographic recording. Moreover, the use of orthogonal system of leads allows assessment of local changes of EG curve morphology as well as spatial analysis of the heart electrical activity such as three-dimensional vectocardiogram [25]. An example of original record is illustrated in Fig. 5.

8.2 Monophasic action potential

The monophasic action potential (MAP) represents the transmembrane potential as measured from the exterior of the cell [58]. Its duration provides information about the repolarization phase of cardiac cycle. The abnormalities in MAP duration may lead to ventricular arrhythmia formation [58]. The MAP can be recorded directly from the surface of the isolated heart. Nowadays, two major approaches are possible: electrical measurement using suction or floating electrodes (single-point measurement) [11] or optical measurement using a single photodetector (single-point measurement) or image sensor (area measurement).

Electrode-based methods do not differ from the EG recording. The main disadvantage is the local tissue damage caused by suction or suturing the electrodes to the heart muscle, which may lead to local changes in conduction of electrical stimuli [7]. Mechanical vibrations and heart movements are usually not strong enough to affect the quality of the recording or even to loose electrical contact. The disadvantage of this electrode is the short-term record. Signals recorded from suction or floating electrodes represent summation of action potentials from a bundle of surrounding cardiomyocytes and reproduce more or less the expected propagation and shape of the action potential in the area of interest.

Optical methods allow touchless recording from a single spot or larger area based upon the technology used [10]. All these methods are based on application of fluorescent voltage-sensitive dye in the examined tissue for defined period of time and exposing the tissue to the excitation light with preselected spectrum. It leads to excitation of dye molecules bound to the cell membrane to higher energetic state and subsequent light emission. The spectrum fluorescence light emitted by voltage-sensitive dyes is proportional to the transmembrane potential [31]. The emission spectrum of the dyes is typically shifted due to the decreased energy by the return to the ground energy state [14, 47]. This spectral response is fast enough to detect transient potential changes in excitable cardiac cells. Excitation and emission lights pass through optical filters and/or dichroic mirrors to separate spectral bands corresponding to the excitation and emission levels of the fluorescence dye [28, 29]. The photodetector transforms light to an electrical signal, which can be acquired, digitized, and archived using a computer with standard signal processing acquisition card working at selected sampling frequency (usually from 500 Hz up to 4 kHz).

Fast and simple systems consist of a source of light [halothane lamp, xenon/mercury arc lamp, high-power light emitting diode (LED), or laser] [46], a single photodiode detector with a front-end high-pass optical filter followed by an analog amplifier, an analog anti-aliasing low-pass filter, and a high-pass filter to suppress DC offset. Excitation light from the lamp/laser is usually transmitted by a flexible fiber bundle cable. Emitted fluorescence light is then collected by a single detection fiber connected to a light detector. The light sources contain a built-in infrared filter, which prevents the isolated organ of heating, and a band-pass filter, which selects the light at excitation peaks of the fluorescent voltage-sensitive dye used (Fig. 6) [44].

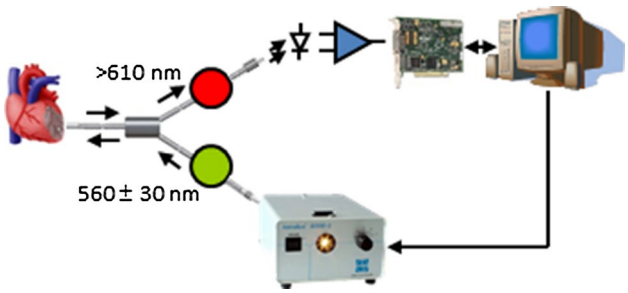

Fig. 6 Recording system developed by the authors. Bifurcated flexible fiber cable FCR-7IR200-2-ME (Avantes, the Netherlands) with seven optical fibers 200 μm in diameter each (six illumination fibers and one detection fiber positioned in the center of the cable). The "input" fiber is connected to a 90-W halogen light source Intralux (Volpi AG, Switzerland) that contains a built-in IR filter and a band-pass filter (560 ± 30 nm). The "output" (detection) fiber is connected to Si photodiode 3 WK 164 87 (Tesla Blatna, Czech Republic) with a high-pass (>610 nm) filter. The electrical circuits include an anti-aliasing filter (fc = 2 kHz) and a high-pass filter (fc = 0.05 Hz). LabVIEW compatible data acquisition multifunction card PCI-6111E (National Instruments, USA) digitizes the signal with 12-bit dynamic range and at rate of 4000 samples/sec. The used voltage-sensitive dye: di-4-ANEPPS (Molecular Probes, USA)

Slower but more complex systems require different way of excitation of the heart tissue from distant places located around the heart. The reason is that the image must be acquired from a larger area of the tissue. Generally, two approaches are used: oriented flexible fiber bundle attached to the heart surface with an image area sensor on the other end or a fixed optics camera positioned around the heart or around the bath with the immersed heart [12, 23]. In the first approach, heart movement does not influence the recording procedure as the flexible fiber bundle "floats" with the heart wall. In the second approach, fixation of the heart and "flattening" the heart surface by compression of the organ against flat glass inner surface of the bath are required. Thus, heart movement is eliminated, and image can be acquired using standard (fast) optical or fluorescence camera. Other techniques require more sophisticated software methods to eliminate movement directly in the acquired digital images by matching images each against other [54].

8.3 Intracellular calcium concentration $[Ca^{2+}]_i$

The systems designed for recording monophasic action potentials described above can also be used to measure the dynamic changes of the intracellular calcium concentration $[Ca^{2+}]_i$. Calcium-sensitive fluorescent dyes serve as indicators with spectra varying in response to Ca^{2+} acceptance. These dyes are classified into following groups based on their spectral properties [55]: dyes with excitation in ultraviolet (indo1, fura2) and visible ranges—blue, green, and red (fluo3, calcium green, rhod2), non-ratiometric (fluo3, fluo4, calcium green dyes, and rhod2), and ratiometric (indo1, fura2, and fura red) dyes; and dyes with emission in blue (indo1), green (fura2, fluo3, indo1, and calcium green), yellow and orange (rhod2), and red and near infrared (fura red) [46] wavelengths.

Relative changes in $[Ca^{2+}]_i$ are measured using non-ratiometric dyes with non-shifting excitation and emission spectra of calcium-saturated dye molecules, which only change their emission fluorescence intensity toward larger values upon binding to calcium. The most used non-ratiometric dyes, fluo3 and fluo4, have similar structures and emission spectra. After calcium binding, the changes of fluo3 emission can be 40–100 times higher than those of calcium-free dye [26]. The response of fluo4, however, is greater: intensity of fluo4 emission is up to twice that of fluo3 [26]. Thus, lower fluo4 concentrations can be used to generate an optical signal with the same intensity [18] (fluo3 is more phototoxic to cells than fluo4 [18]) and some other non-UV dyes [49].

Ratiometric measurement of $[Ca^{2+}]_i$ yields better results as well as ratiometric AP measurement. There are two kinds of dyes: ratiometric in emission and ratiometric in excitation. The former (e.g., indo1) is often achieved using one light source (due to overlapped excitation spectra of Ca^{2+}-bound and Ca^{2+}-free dye molecules) and two photodetectors that allow truly simultaneous recordings. Measuring with the latter (fura2, fura red) requires switching of excitation filters (for excitation of Ca^{2+}-bound and Ca^{2+}-free dye molecules) and synchronization of emission light detection (due to overlapped emission spectra of Ca^{2+}-bound and Ca^{2+}-free dye molecules).

For better understanding of calcium handling and its arrhythmogenic role, simultaneous measurement of intracellular calcium content and membrane voltage is at hand [6, 61].

9 Mechanical activity

Spread of depolarization wave across the heart results in mechanical responses of the cardiac contractile elements, resulting eventually in a contraction of the whole heart. The easiest assessment of contractile force in isolated heart may be realized simply by attaching the heart to a diverting roll [11]. For more exact assessment of contractile force, namely on small size heart like murine [53] or neonatal rat heart [45], the left ventricle pressure is measured. The deflated balloon-tipped catheter is inserted into the left ventricle through the artificial orifice in the left atrium. After filling the balloon with fluid, the changes of the pressure in the left ventricle are continuously recorded and converted by a pressure transducer to the electrical signal. In the Neely model, the left ventricle is filled with the perfusion fluid and the balloon catheter measurement of the ventricular pressure is impossible—monitoring of changes of the left ventricular pressure is thus achieved using piezoelectric crystal on the tip of catheter located in the left ventricle. It is possible to insert the catheter to left ventricle through aortic cannula or via a punctation in apical part of the left ventricle. Both options minimize possible damage of the heart tissue by cutting an orifice in the left atrium.

The increment of the interventricular balloon volume in Langendorff model or changing the loading conditions in isolated working heart and monitoring the subsequent left ventricular pressure changes allow the generation of the Frank–Starling curve as an indicator of contractility [42, 43]. Pressure and volume of the left ventricle in the isolated working heart model can be also continuously monitored by the conductance catheter, containing several ring electrodes along its length. A high-frequency low-amplitude constant current is passed through the outer electrodes to generate an electric field. The potential difference between any pair of inner electrodes is inversely proportional to the amount of conductive material at that site [38]. The pressure–volume loop is reconstructed from this record and

further analyzed. End-systolic pressure–volume relationship (ESPVR) and its slope as well as end-diastolic pressure–volume relationship (EDPVR) and its slope are subsequently obtained. ESPVR and its slope describe systolic function of left ventricle and provide information about myocardial contractility, while EDPVR and its slope provide information about passive ventricular filling and stiffness during the diastolic phase of cardiac cycle [24]. The advantage of isolated working heart is exact control of preload which allows studying of pressure–volume relationship in strictly defined and controlled cardiac loading conditions [1, 19, 24].

10 Conclusion

More than a century from its introduction, the isolated heart model still represents golden standard in basic cardiovascular research. The possibility to record a broad spectrum of electrical, mechanical, and biological parameters from a single experiment makes it feasible to comprise the whole range of studies in physiology, pathophysiology, pharmacology, and toxicology.

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