Chapter 39

Non-optogenetic approaches for leadless cardiac pacing: mechanically induced excitation for extracorporeal control of cardiac rhythm

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39.1 Introduction

Implantable electrical pacemakers are a corner-stone of modern heart rhythm management [1]. Since their clinical introduction in 1958, their technological sophistication, both in software (e.g., programmability, adaptability, automaticity, and associated algorithms) and hardware (e.g., battery, sensor, and lead technology), and their indications for use (e.g., atrioventricular block, bradycardia, heart failure, arrhythmias, hypertrophic cardiomyopathy, etc.) have steadily increased [2]. As a result, by 2009–14 pacemaker implantation had increased to approximately 60 implantations per 100,000 persons in the United States [3] and Canada [4], and slightly less in Europe (approximately 50 per 100,000 persons, although this varied greatly by country, with the highest countries [Germany, Finland] having rates above 100 per 100,000 persons) [5].

Despite their incredible utility, inherent limitations (e.g., infection, thrombosis, generator or lead failure, lack of autonomic responsiveness, interactions with magnetic fields) motivate exploration of alternative pacing modes. This has included the development of biological and leadless pacemaker systems, however even these potentially transformative technologies are limited in certain settings, due to the need for (minimally invasive) surgical implantation.

In the emergency setting, the bradycardic or asystolic heart can be a life-threatening condition. In this case, a method for extracorporeally induced pacing for use during resuscitation, transportation, or as a bridge to permanent pacemaker implantation has the potential to be a life-saving intervention. A commonly used technique of temporary pacing for emergency cases is transcutaneous electrical pacing through the chest wall [6]. However, this technique is painful, not practical for prolonged use, and typically necessitates the use of a sedative or aesthetic agent, which may further impair the critical hemodynamic condition of a patient. Mechanical pacing, on the other hand, represents a rapidly available, non-invasive, and generally well-tolerated means of pacing the asystolic [7] or bradycardic [8] heart, which has been used to maintain consciousness in patients during extended asystolic periods (close to 3 hours in some cases) [9]. In this chapter, the mechanisms, application, challenges, and future directions of mechanical pacing will be reviewed and discussed.

39.2 Mechanisms of mechanical pacing

39.2.1 Mechano-electrical coupling

The heart's mechanical activity and its environment and are tightly linked to its electrical activity. This relationship involves feed-forward connections between electrical excitation and mechanical contraction (commonly known as excitation–contraction coupling) [10] and feed-back from the mechanical state of the myocardium to the origin and spread of excitation (mechano-electric feedback) [11]. These links form an intracardiac mechano-electric regulatory loop (mechano-electric

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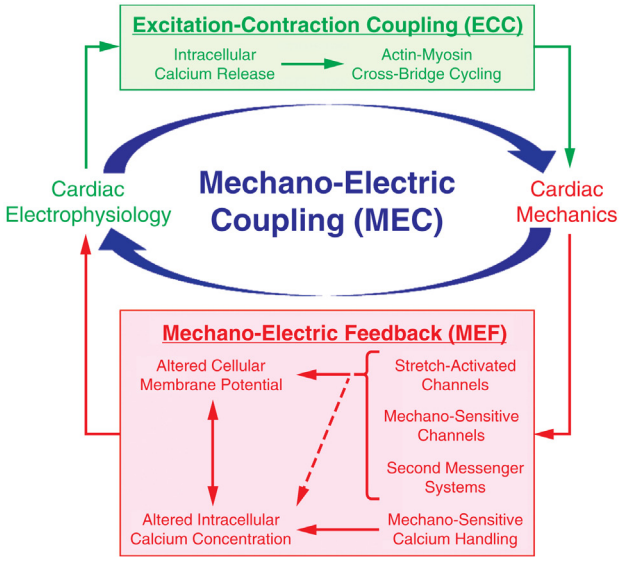

FIGURE 39.1 The Mechano-Electric Coupling (MEC) regulatory loop. Feed-forward (excitation–contraction coupling, ECC) and feedback (mechano-electric feedback, MEF) links between cardiac mechanics and electrophysiology. *Reproduced with permission from Quinn [117].*

coupling, MEC) driven by multiple-mechanisms, including specialized stretch-activated ion channels, ion channel mechano-sensitivity, intracellular calcium handling, and second messenger systems (Fig. 39.1) [12]. MEC is apparent at all levels of structural and functional integration, from the (sub-)cellular to whole organ and in patients and may be important both for normal cardiac function [13] and in deadly cardiac arrhythmias [12]. As a result, acute localized mechanical stimulation of the heart, for instance during finger-tapping of the epicardium in open heart surgery, by direct tissue contact of intra-cardiac catheters [14–16] (Fig. 39.2) and pacing leads [17–19], or by extracorporeal impact with precordial thump [20] can cause mechanically induced excitation, resulting in myocardial contraction.

39.2.2 Determinants of mechanically induced excitation

One of the principal mechanisms thought to underly the response of the myocardium to acute mechanical stimulation is activation of cation non-specific stretch-activated channels (SAC_{NS}), whose open probability is increased in response to cell deformation [21]. SAC_{NS} were discovered in cardiac cells over two decades ago (Fig. 39.3) [22,23]. With a reversal potential between peak and resting membrane potential levels (~-20–0 mV) [24], the timing of acute mechanical stimulation is critical to outcome, as when SAC_{NS} are opened membrane potential will be dawn to this potential [21]. As a result, when applied during diastole, activation of SAC_{NS} by acute mechanical stimulation will cause membrane depolarization, which, if supra-threshold, will trigger excitation (Fig. 39.4) [25]. On the other hand, SAC_{NS} activation in systole during the action potential plateau will have a repolarizing effect, causing action potential shortening [26].

Experimentally, stretch-induced depolarization of resting membrane potential has been demonstrated in isolated cells [27], tissue [28], and whole heart preparations [29]. In one of the classic illustrations of MEC, it was shown that in isolated canine hearts a transient increase in the volume of an intraventricular balloon causes diastolic depolarization, whose

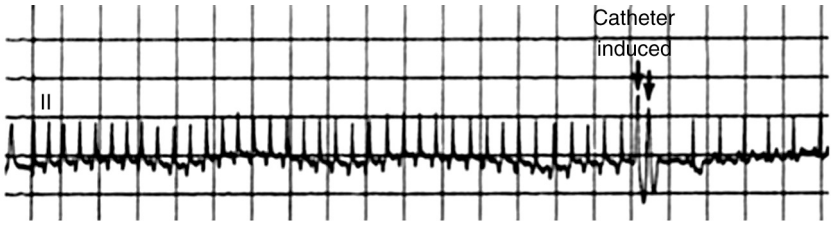

FIGURE 39.2 Acute localized mechanical stimulation of the heart by an intra-cardiac catheter. ECG lead 2 from a patient undergoing right cardiac catheterization, showing two premature beats as the catheter is withdrawn from the pulmonary artery into the right ventricle. *Reproduced with permission from Befeler [14].*

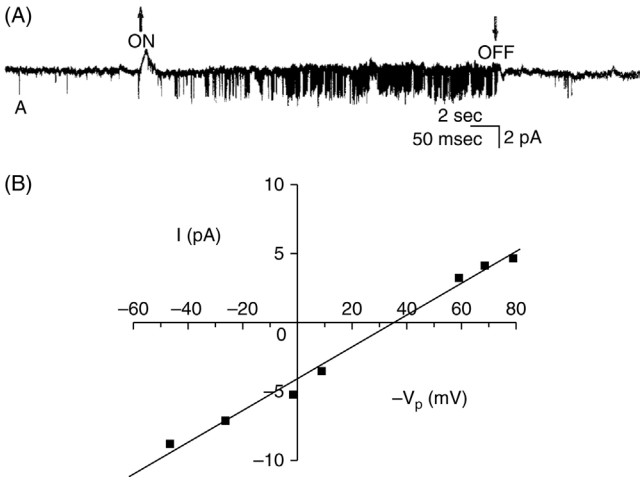

FIGURE 39.3 Cation non-specific stretch-activated channels (SACNS) in cardiac cells. (A) Cell-attached patch recording of a neonatal rat ventricular myocyte during application of negative pressure (~2 cm Hg). (B) Current (I)-voltage (V_p) relationship of resulting stretch-activated current. *Reproduced with permission from Craelius et al. [22].*

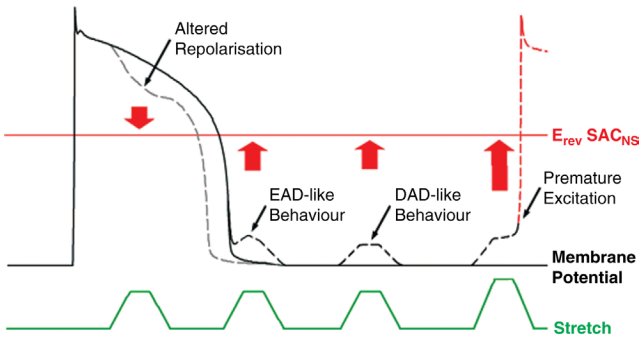

FIGURE 39.4 Schematic representation of transient effects of stretch on ventricular membrane potential. Indication of contribution by cation non-selective stretch-activated channels (SAC_{NS}; red arrows), based on SAC_{NS} reversal potential (E_{rev}; red line). Depending on stretch timing, the action potential may be shortened (grey dashed line), or the cell may depolarize (black dashed line), resulting in early (EAD) or delayed (DAD) after-depolarization-like behavior, and with sufficient stretch excitation (red dashed line). *Adapted with permission from Kohl [125].*

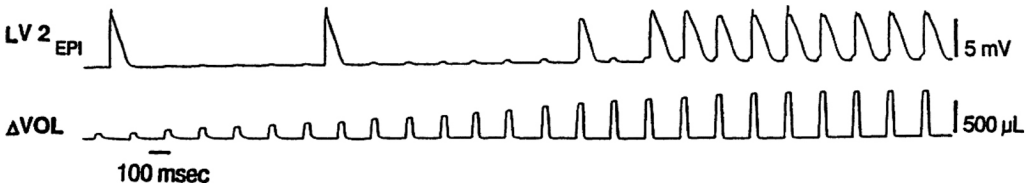

FIGURE 39.5 Effects of transient whole heart stretch by intraventricular balloon inflation. Monophasic action potential (MAP) recordings form the epicardium (EPI) of the left ventricle (LV) of an isolated canine heart during transient changes in LV volume (ΔVOL). *Reproduced with permission from Franz et al. [29].*

amplitude correlates with the magnitude of the volume applied [30]. If sufficiently large, these mechanically induced depolarizations can trigger premature ventricular beats (Fig. 39.5) [29]. This response was attributed to SAC_{NS}, as their pharmacological block eliminates the response [31]. It was further suggested that it was the myocardial deformation (rather than an increase in myocardial stress) that was the determining factor for supra-threshold depolarization, as the change in intraventricular volume that caused mechanically induced excitation was remarkably consistent between experiments in the same species, while the associated changes in intraventricular pressure showed high variability [32].

Local mechanical stimulation of the ventricles is also effective for causing premature beats. In a recent study of mechanisms of arrhythmogenesis in *Commotio cordis*, it was shown with voltage optical mapping that local mechanical stimuli applied to the epicardium of isolated rabbit hearts reliably triggers premature excitation at the contact site, which is similar to electrically induced excitation (Fig. 39.6) [33]. Further, in agreement with the results from global mechanical stimulation, excitation-inducibility was predicted by local tissue deformation (rather than tissue stress, applied force, or rate of deformation), and was eliminated by pharmacological block of SAC_{NS}. Similar results have been shown in monolayers of cultured cardiac myocytes stimulated with fluid jets [34], in which optical mapping revealed local excitation that was reduced with SAC_{NS} block, and in a pig model of *Commotio cordis*, in which precordial impact resulted in focal excitation originating from tissue immediately underneath the site of impact (Fig. 39.7) [35].

Thus, it is clear that mechanically induced deformation of the heart can result in localized depolarization of membrane potential, leading to mechanically induced premature excitation, an effect that is determined by the extent of myocardial deformation and is caused by SAC_{NS} activation.

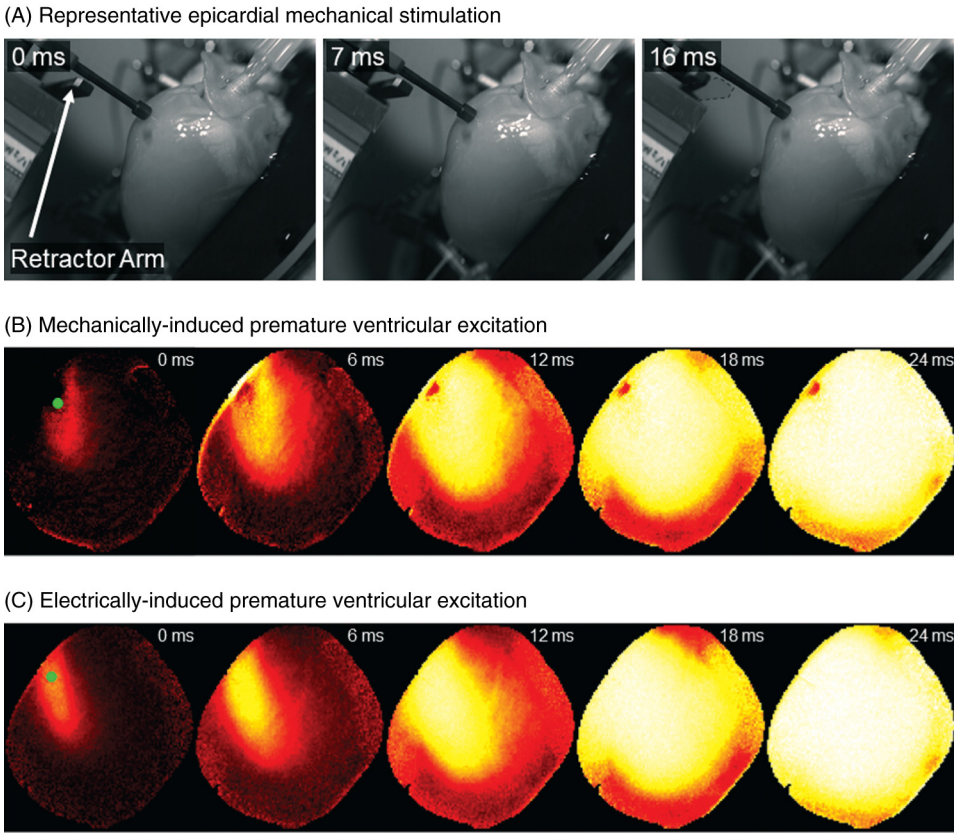

FIGURE 39.6 Local epicardial mechanical stimulation and left ventricular excitation visualized by optical mapping. (A) Images of local epicardial mechanical stimulation applied to the left ventricle of an isolated rabbit heart. (B and C) Representative voltage optical mapping recordings during mechanically (B) or electrically (**C**) induced excitation from the same mid-level freewall location (green dot). *Reproduced with permission from Quinn et al. [33].*

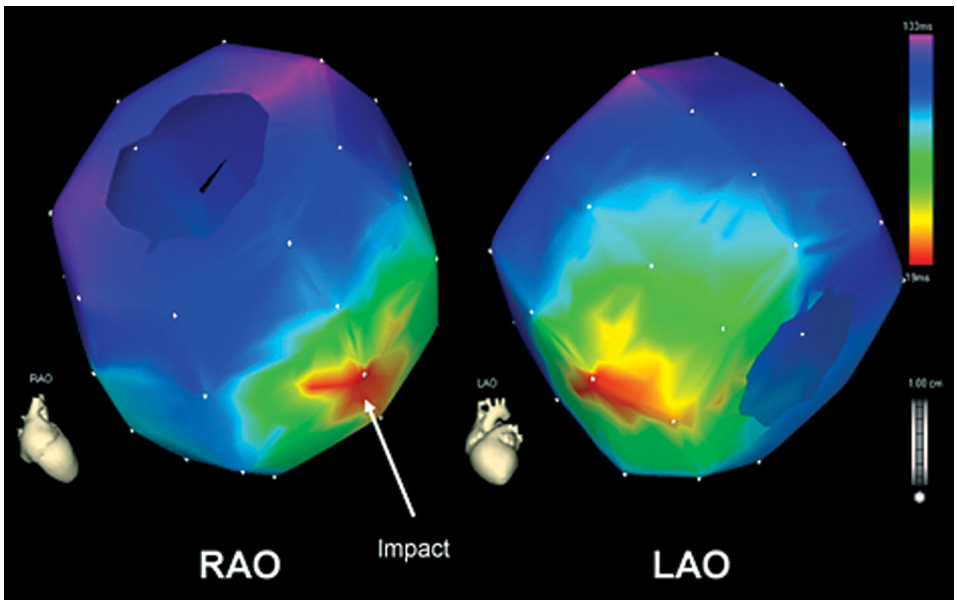

FIGURE 39.7 Mechanically induced excitation during precordial impact. Map of endocardial activation from a 64-pole constellation basket in the left ventricle of a sedated pig. *Reproduced with permission from Alsheikh-Ali et al. [35].*

39.3 Application of mechanical pacing

39.3.1 Precordial percussion

Nearly one hundred years ago, using rhythmic application of fist thumps applied to the precordium (now commonly referred to as "precordial percussion," "percussion pacing," or "fist pacing") (Fig. 39.8A), Eduard Schott triggered competent ventricular contractions in patients with acute Stokes-Adams attacks (characterized by a decrease in cardiac output and loss of consciousness due to a transient arrhythmia - often an asystolic or bradycardic ventricle) allowing them to sustain consciousness for extended periods of time [20]. The potential for extracorporeal mechanical pacing as an emergency intervention, however, was given little attention (aside from a paper in 1960 [36] and a case report in 1963 [7] on its use in asystole). It was not until 1970, when a paper detailing the first use of precordial thump to defibrillate the tachycardic heart was published [37] that there was a renewed interest in precordial percussion pacing [38], which led to discussion and dispute about its utility [39,40].

Since then there have been no prospective clinical studies of precordial percussion pacing [41], but a number of case reports have shown its ability to effectively mechanically pace the bradycardic or asystolic heart for extended periods (Fig. 39.8B) [7–9,42–52]. In the few case series of precordial percussion pacing reported in the literature, a total of 139 patients have been mechanically paced, with a 93% success rate [53–55]. Importantly, ventricular contractions resulting from extracorporeal mechanically induced excitation have been shown to be hemodynamically more productive than external chest compressions used in cardiopulmonary resuscitation (cardiac output is 77% of baseline for mechanically induced excitation, compared to 38% with optimally performed chest compressions) [56,57].

Two experimental studies have investigated the utility and mechanisms of precordial percussion pacing. In an anesthetized pig study of the potential of precordial thump for terminating ventricular fibrillation, while precordial thump failed as a means for defibrillation (necessitating the use of electrical defibrillation), in the asystolic post-shock period precordial percussion was an effective means of pacing the heart (Fig. 39.9), with the success of mechanically induced excitation being associated with thump-induced left ventricular pressure [58]. In a microminipig model of cardiac standstill (created by inducing complete atrioventricular block by catheter ablation), the efficacy of precordial percussion pacing was compared to standard chest compressions and ventricular electrical pacing [59]. Precordial percussion was able to pace the heart continuously for up to 2 hours, and similar to findings in patients [56,57], it was shown that precordial percussion was hemodynamically similar to ventricular electrical pacing, unlike chest compressions, with which hemodynamics were compromised. Further, it was shown that the non-selective stretch-activated channel blocker amiloride decreased the incidence of ventricular excitation with precordial percussion, suggesting that SAC_{NS} are involved. Interestingly, it has also been shown in pigs [60] (and patients [61]) that chest compressions can lead to ventricular excitation, resulting in mechanical pacing of the heart (Fig. 39.10A).

The potential for using precordial percussion as a means for extracorporeal pacing led pacemaker, defibrillator, and resuscitation pioneer Paul Zoll to develop a device for temporary mechanical pacing [55]. The device ("cardiac thumper") was a

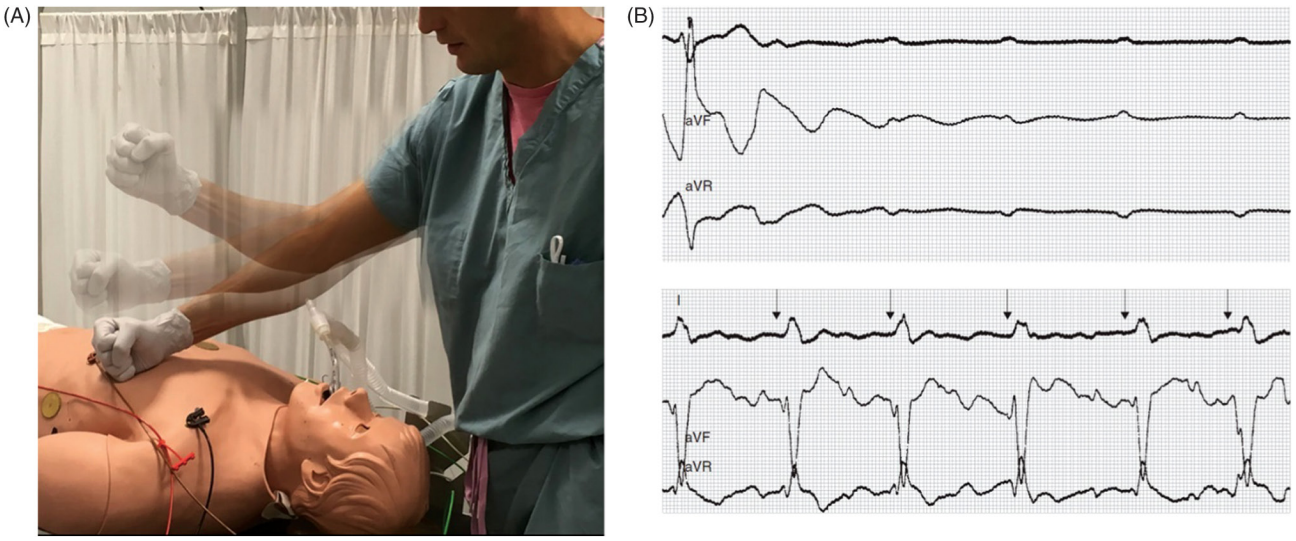

FIGURE 39.8 **Precordial percussion pacing.** (A) Technique of percussion pacing, using serial blows with the ulnar side of the clenched fist to the lower left sternal edge. *Reproduced with permission from Giordano et al. [47]* (B) Complete heart block with ventricular asystole in a patient during cardiac catheterization (upper panel), followed by broad QRS complexes at a rate of 80 bpm induced by percussion pacing (indicated by arrows). *Reproduced with permission from Eich et al. [44]*

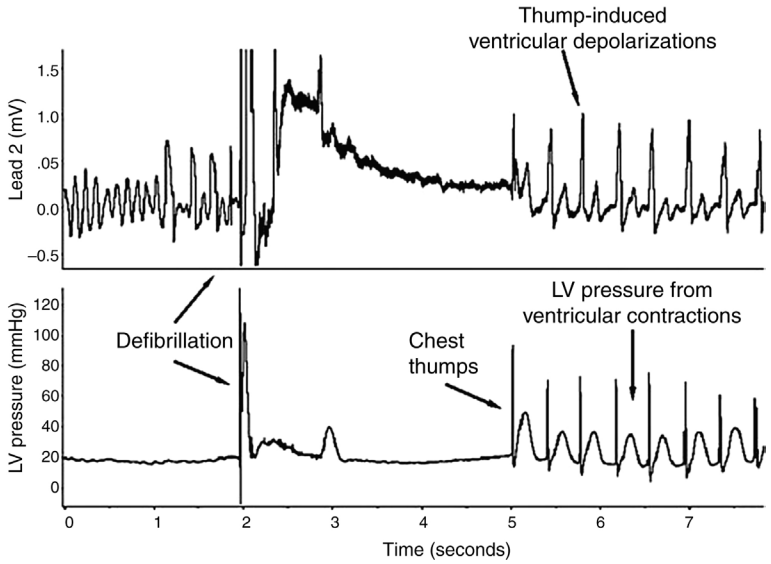

FIGURE 39.9 Precordial percussion pacing in the experimental setting. Termination of ventricular fibrillation by external defibrillator shock in an anesthetized pig, followed by a single premature ventricular contraction, two seconds of asystole, and a series of chest thumps resulting in ventricular depolarization that produce left ventricular (LV) contraction. *Reproduced with permission from Madias et al. [58].*

modification of an industrial stapling gun, that could be manually operated or triggered by the R-wave of the electrocardiogram for synchronization of mechanical stimulation with phases of the cardiac cycle. This device had the advantage of being less painful than transthoracic electric stimulation, the standard-of-care method for temporary extracorporeal pacing at the time, as well as requiring less energy (0.04–1.5 J) than even modern external defibrillators (150–360 J) [62]. This device was tested in dogs with normal sinus rhythm or atrioventricular block, which demonstrated that repetitive heartbeats could be evoked. The device was also shown to be effective in 10 patients with asystole after ventricular fibrillation, with atrial fibrillation, or with implanted pacemakers for atrioventricular block. Ultimately however, the device was considered uncomfortable by patients, which limited its prolonged clinical use and resulted in it being quickly superseded by advances in external electric stimulation [63].

39.3.2 High intensity focused ultrasound

While precordial percussion is an immediately accessible form of extracorporeal pacing that is well suited for out-of-hospital emergency settings, more recent device-based mechanical pacing efforts have focused on the use of extracorporeal high intensity focused ultrasound (HIFU) [64]. An effective ultrasound-based pacing device would have the clear advantage over percussion pacing of being more comfortable for the patient and being useful over a longer period.

The bioeffects of ultrasound have been extensively studied, motivated by the assessment of its safety for use in echocardiography. Effects are dependent on tissue properties (e.g., density, attenuation, absorption), ultrasound exposure parameters (e.g., frequency, intensity, pulse duration/duty cycle), and beam configuration [65]. In general, the bioeffects of ultrasound may be categorized as thermal or mechanical. Thermal effects are a result of absorbed ultrasound energy being converted into thermal energy, causing heating of the tissue, which if excessive can cause tissue damage. Mechanical effects relate to either physical deformation of tissue/cells or to tissue cavitation. Cavitation is a process by which microscopic gas bubbles develop in an acoustic field at high negative pressures, vibrate, and with enough acoustic pressure implode, causing microscopic regions of high temperature and tissue damage. Cavitation can be enhanced by the use of contrast microbubbles, which can then result in cardiac excitation [66–71] (through activation of SAC_{NS} [72]), with a positive correlation existing between the incidence of ultrasound-induced premature excitation and the resulting tissue damage [73–77]. Ultrasound-induced tissue deformation, on the other hand, can occur as a result of acoustic radiation force, which is a consequence of momentum transfer from the ultrasound wave to the tissue, created by acoustic energy attenuation. In fact, mechanically induced excitation of the heart by extracorporeally generated shock waves commonly occurs during lithotripsy and is one the known complications of the procedure [78–84]. At a microscopic level, ultrasonic waves may also cause direct mechanical vibration of cellular structures [85], which could excite SAC_{NS}, resulting in cellular excitation.

The first report of the excitatory effects of ultrasound on the heart came from E. Newton Harvey in 1929, who noted that in frog and turtle hearts high frequency ultrasound caused an increase in beating rate or in the regular beating of an otherwise quiescent ventricle[86]. Subsequent studies showed similar ultrasound-induced excitation in frog [87], mouse [88], and rat [89] hearts, as well as cultured neonatal ventricular cardiomyocytes [90].

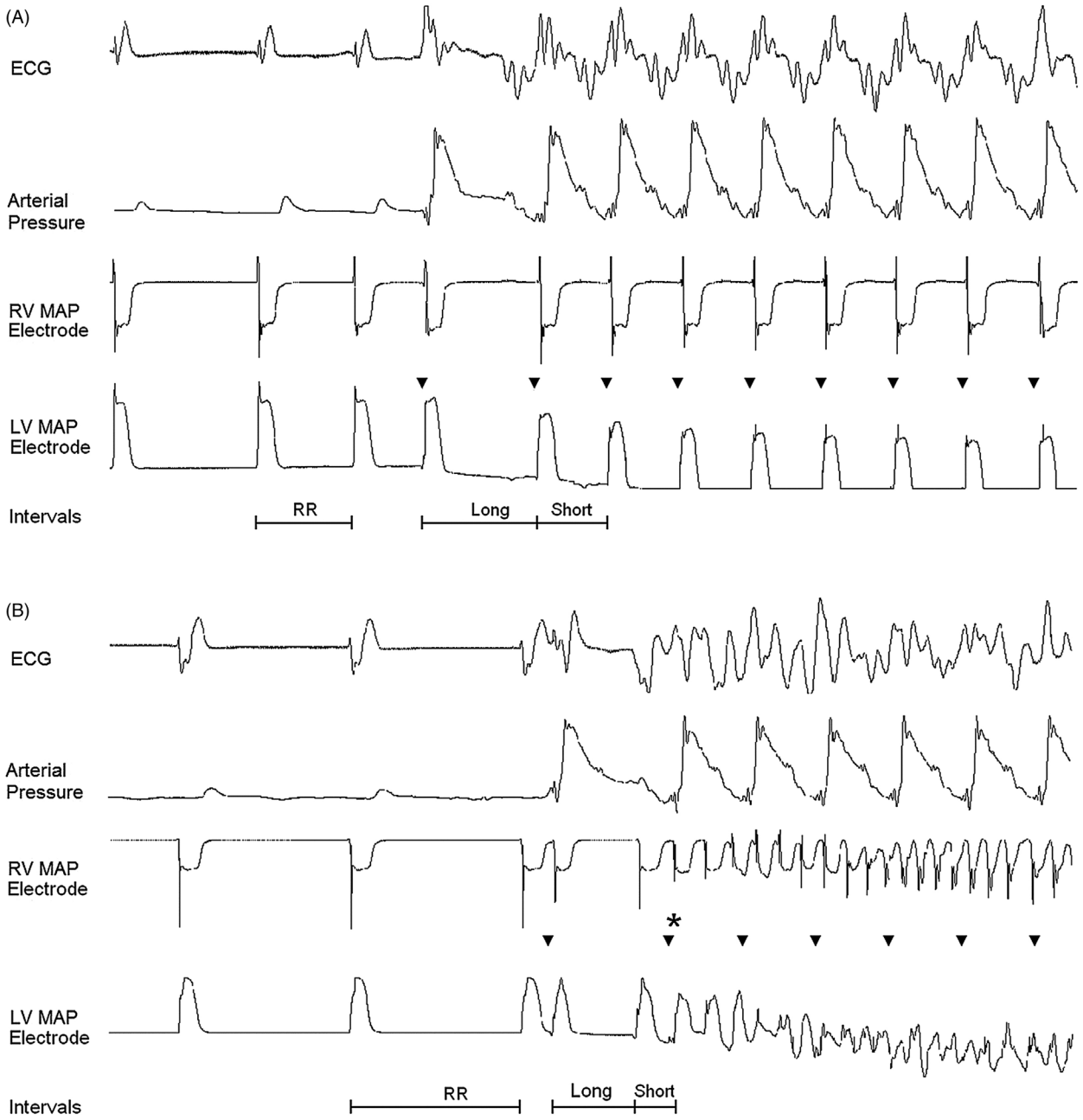

FIGURE 39.10 **Cardiac stimulation by precordial chest compressions.** (A) 1:1 ventricular excitation in an anesthetized pig (shown in right [RV] and left [LV] ventricular monophasic action potential [MAP] recordings) during mechanical chest compressions (marked by arrows) after long-lasting (at least 2.5 minutes) ventricular fibrillation. (B) Ventricular excitation during two mechanical chest compressions (marked by arrows, with an interposed spontaneous depolarisation), immediately followed by ventricular fibrillation. *Reproduced with permission from Osorio et al. [61].*

The first report of repetitive sound wave-induced excitation that might be considered as mechanical pacing was in open-chest anesthetized pigs, using periodic pulses of intense ultrasonic waves generated by an intracavitary transducer consisting of piezoelectric ceramic disks. The application of these ultrasonic waves (70 kHz with 5 ms duration at 5 MPa) to the exposed myocardium resulted in pacing the animals out of hypoxia-induced bradycardia, with nearly 100% pacing capture observed when ultrasonic pressure level or pulse duration was increased [91].

More recently, the first detailed description of HIFU-based pacing was published, in which extracorporeal cardiac pacing was demonstrated in an intact, anesthetized rat model [92]. This system utilized a two-phase sequence of accentuated negative (rarefaction) and positive (insonation) pressure transmission through dynamic adjustment of frequency, phase, and intensity of the HIFU signal, transmitted by a three element, dome-shaped, annular transducer (Fig. 39.11A). This pattern of HIFU application first produces cavitation-related microbubbles in the acoustic focal region by rarefication

(1 ms of 1.8 MPa peak negative pressure with a pulse repetition frequency of 20 kHz and a 28% duty cycle), which enhances the effect of the immediately following ultrasonic shock by isonation (5 ms of a 3 MPa peak positive pressure) (Fig. 39.11B). The insonation was synchronized with the respiratory cycle and the peak of the ECG R-wave, with application timing varied through ventricular diastole (Fig. 39.11C). Using echocardiography for direct visualization of the left ventricle, HIFU-induced contractions were observed (Fig. 39.11D). Overall, the mean success rate for all pacing attempts (using delays of 100–400 ms after the R-wave) was only 12%, but success varied depending on the timing of the HIFU pulse during diastole, with success rates of 25%–50% and up to seven consecutive captured beats obtained in late diastole (450–470 ms delay). Overall, while the rate of HIFU pacing success was modest in this study, it was believed that this was primarily a function of the relatively high heart rate of the rat, and that higher success would have been seen in larger mammals with slower heart rate and a longer diastolic period (such as the previous report in pigs [91]).

The latest published experimental study of HIFU-based pacing was performed in ex vivo and in vivo pig hearts [93]. In this study a 256-element phased array HIFU transducer delivered negative pressure pulses (5 ms, 1 MHz, 5 MPa peak negative pressure) to the right atrium or right or left ventricle, timed from local electrograms. In the ex vivo heart, HIFU stimulation resulted in success over drive pacing (Fig. 39.12A). Further, it was shown that dual chamber pacing of the right atrium and right ventricle was possible with a variable atrioventricular delay, like electrical dual chamber pacemakers, enabled by the beam steering capabilities of the phased-array transducer (Fig. 39.12B). The feasibility of HIFU-induced

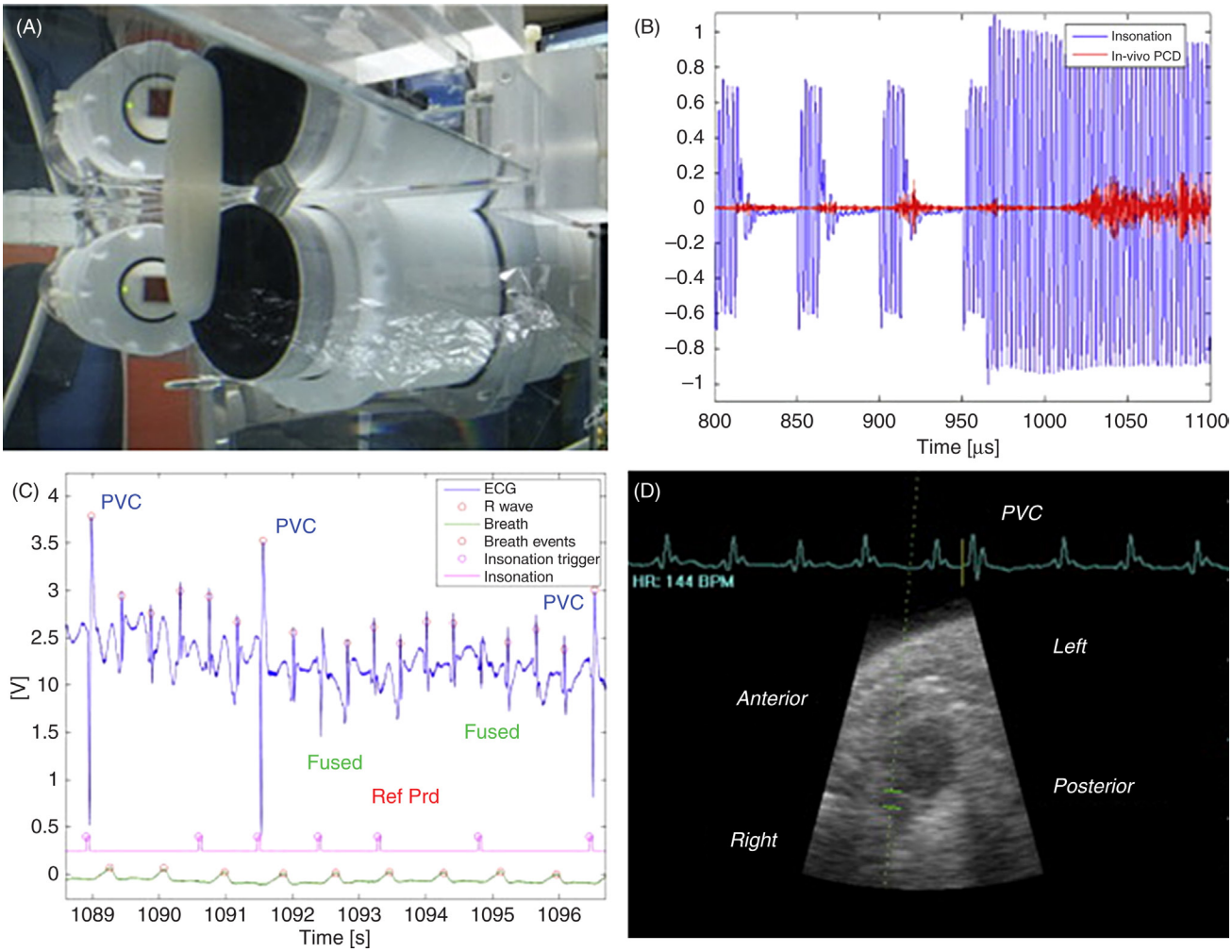

FIGURE 39.11 Extracorporeal high intensity focused ultrasound (HIFU)-based pacing. (A) Experiment setup showing gel phantom, along with the HIFU and ultrasound imager (to its right and left, respectively) and the passive cavitation detector (PCD) aimed at the HIFU focus (tip located at one o'clock relative to the HIFU's face). (B) HIFU base harmony *(blue)* and PCD *(red)* signals during HIFU application. (C) A sequence of premature ventricular contractions (PVCs) induced by extracorporeal HIFU pacing using breath gating to trigger pacing with expiration, shown in the ECG trace (top), along with the insonation triggers (center, marked by *circles*) and breath trace (bottom). (D) Ultrasound image of the left ventricle showing the HIFU focus *(green cursers)* and a mechanically induced PVC on the ECG trace. *Reproduced with permission from Livneh et al. [92].*

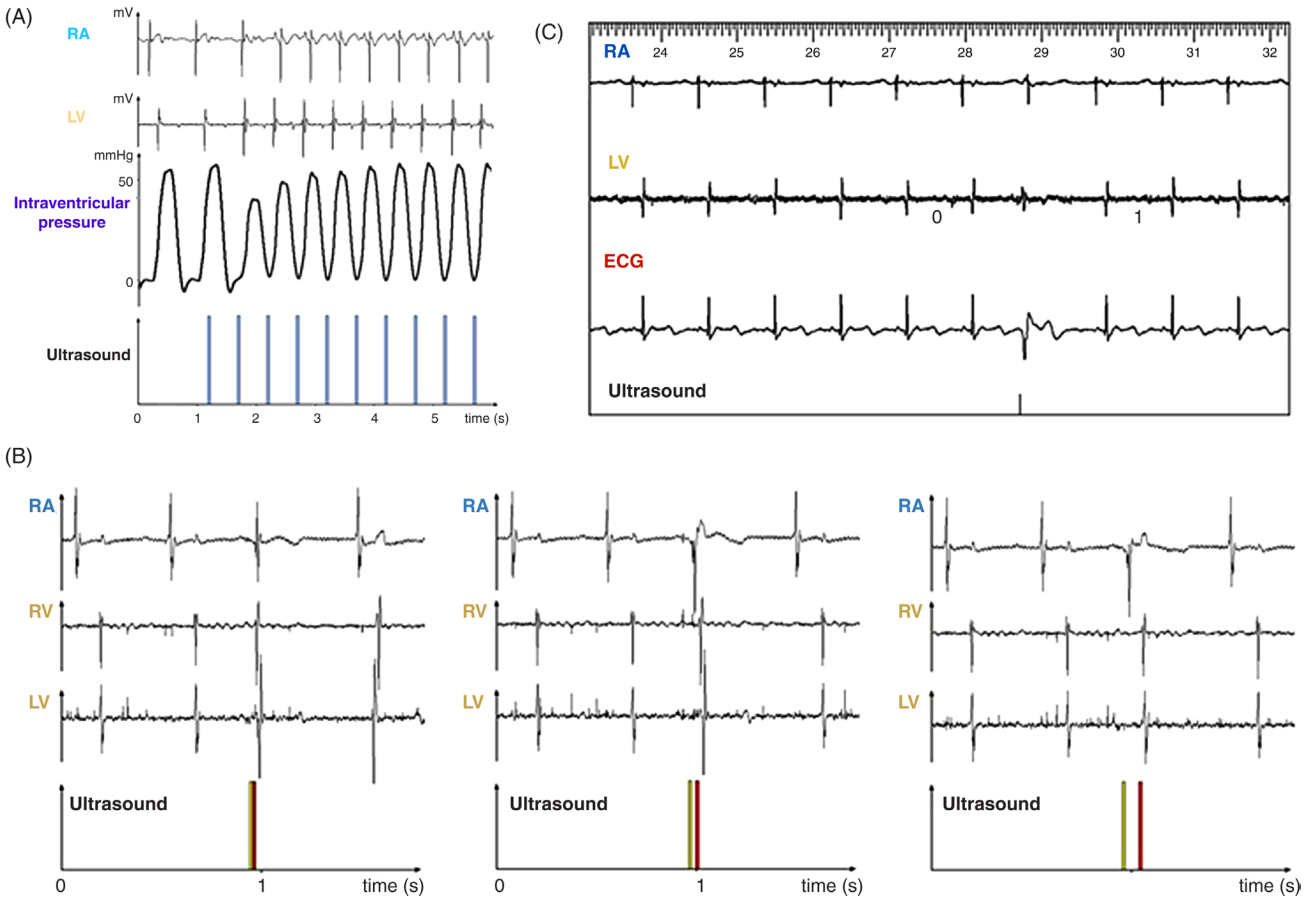

FIGURE 39.12 **Experimental high intensity focused ultrasound (HIFU)-based pacing.** (A) Electrical (right atrium [RA] and left ventricle [LV]) and hemodynamic recordings of continuous ultrasonic pacing of an isolated pig heart. (B) Consecutive stimulation of the right atrium (yellow pulse) and right ventricle (RV; red pulse) with a single ultrasonic probe and an atrioventricular delay of 0 ms (left panel), 40 ms (middle panel), and 120 ms (right panel). (C) HIFU-induced premature ventricular depolarization in an anesthetized pig. *Reproduced with permission from Marquet et al. [93].*

excitation was then tested in vivo, in which it was found that the use of contrast agent was needed to enhance mechanical effects, so that consistent capture was possible (Fig. 39.12C).

39.3.3 Injectable magnetic microparticles

While precordial percussion and HIFU are the forms of non-invasive mechanical pacing with the greatest track record, there have been efforts by others to use alternative modes of energy to extracorporeally excite the heart. Most notably, it has been shown that cardiac excitation can be induced by time-varying magnetic fields [94–100] or by focused near-infrared laser pulses [101]. However, these approaches have thus far proved impractical, due to high energy requirements and unreliable pacing capture. The use of magnetic fields, however, has inspired a recent report suggesting an alternative approach for delivery of mechanical stimulation to the heart using injectable magnetic microparticles [102]. The concept of this study was that intravenously injected magnetic microparticles could be localized and trapped in the cavity of the right ventricle by applying a magnetic force with an external electromagnet. Once in place, generation of an alternating magnetic field that periodically forces the microparticles against the ventricular wall could be used to mechanically stimulate the tissue and cause excitation. This was tested in ex-vivo and in-vivo rat hearts, followed by in vivo experiments in pigs. In the initial Langendorff-perfused isolated rat heart experiments, the electromagnet magnetic (Fig. 39.13A) was positioned directly against the freewall of the right ventricle and a low duty (20%) square waveform was applied (5 Hz, with a 40 ms period of current in the coil, followed by 160 ms without current). Magnetic microparticles (7.6 μm) were then injected directly into the right ventricle, which resulted in overdrive pacing (Fig. 39.13B). Interestingly, sine and ramp protocols were ineffective, highlighting the need for pulsatile mechanical stimulation for mechanically induced excitation to occur. Next, in anesthetized rats with drug-induced bradycardia (using the alpha-2-adrenergic agonist xylazine), the electromagnet coil was

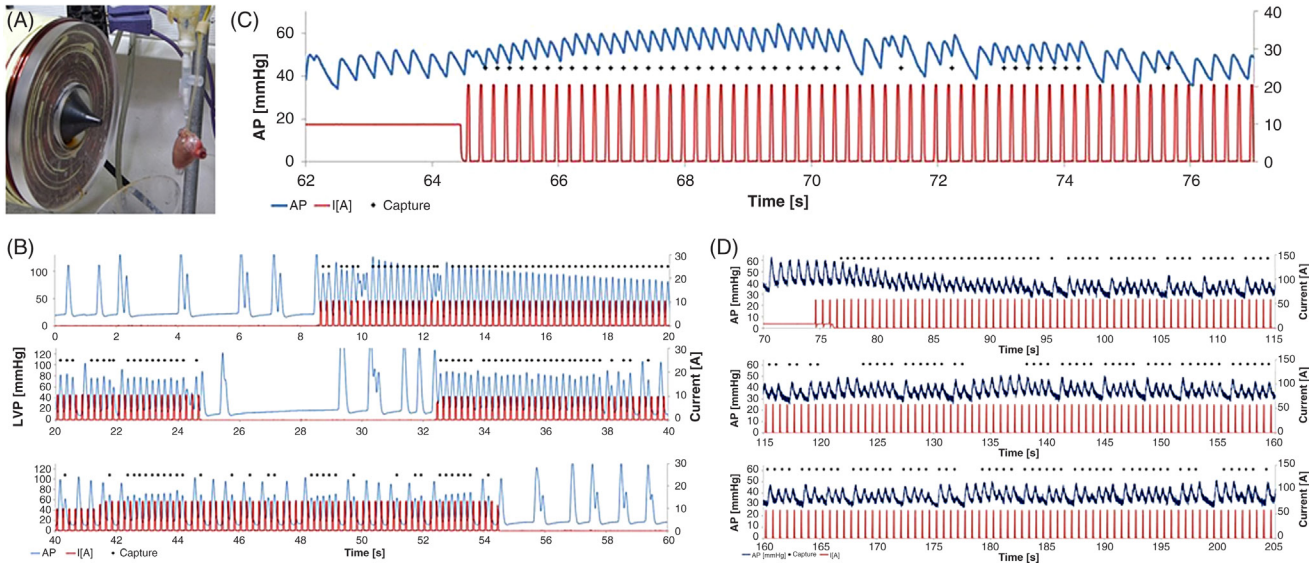

FIGURE 39.13 Mechanical pacing with injectable magnetic microparticles. (A) Electromagnet and Langendorff-perfused rat heart (during mechanical pacing the electromagnet was positioned against the ventricular apex). (B) Mechanical pacing of a Langendorff-perfused rat heart, showing left ventricular pressure (LVP; *red line*), current through the electromagnet coil (I; *blue line*), and mechanically stimulated beats (indicated by *+signs*). (C) Mechanical pacing of an in vivo rat heart. (D) Mechanical pacing of an in vivo pig heart. *Reproduced with permission from Rotenberg et al. [102].*

positioned over the lower part of the sternum and microparticles were injected into the tail vein. After 30–60 seconds, the magnet was switched to generate magnetic pulses with either a low (20%) or high (80%) duty cycle. While stimulation with the high duty cycle was largely ineffective for inducing ventricular excitation, the low duty cycle consistently provoked transient overdrive pacing that lasted for periods of 4–20 seconds (Fig. 39.13C). Finally, in open-chest anaesthetized pigs, the electromagnet was positioned against the right ventricle and the magnetic microparticles were injected into the femoral vein. As in the rats, first the magnetic particles were accumulated in the ventricle by applying a constant magnetic field for ~1 minute, followed by application of short duty cycle (10%) square pulses. While only tested in two pigs, in both cases this strategy resulted in ~20 seconds of sustained pacing, followed by 2 minutes of intermittent excitation (after which the experiment was stopped due to overheating of the electromagnet) (Fig. 39.13D).

39.4 Challenges for mechanical pacing

39.4.1 Loss of mechanical pacing capture

While extracorporeal pacing is clearly possible through methods causing mechanically induced excitation, the techniques developed to date all appear to be unable to sustain continuous pacing over an extended period. In particular, the most developed reports of mechanical pacing using HIFU [92] or injectable magnetic microparticles [102] suffer from rapid loss of capture. In the case of HIFU-based mechanical pacing, hearts responded only a maximum of seven times before losing the ability to consistently respond to mechanical stimuli, despite pacing being limited to once per breathing cycle. Mechanical pacing with injectable magnetic microparticles was marginally more successful, with ~30 beats being captured before loss of 1:1 capture (followed by ~1.5 minutes of sporadic mechanically induced excitation). Moreover, even though clinically mechanical pacing has been reported to be successful over longer periods, in the published cases it is unknown whether there was indeed 1:1 (rather than sporadic) pacing capture, and in many cases, treatment was interspersed with periods of spontaneous circulation, so the sustainability of individual periods of mechanical pacing is uncertain. It is also worth noting that in emergency settings the hearts of patients in asystole will be in a state of global ischemia (with ischemic severity depending on response time), which will impact the efficacy of mechanical stimulation [103], yet all experimental studies to date have been performed in healthy hearts.

The cause of a lack of sustainability in mechanical pacing studies is not clear but has been attributed to a loss of magnetic microparticles [102] or contrast agent at the pacing site [93], or disruption of myocyte homeostasis (such as a mechanically induced increase in intracellular calcium levels) [92]. A recent study of mechanical pacing by direct epicardial mechanical stimulation in rabbit isolated hearts has corroborated the rapid loss of successful mechanical pacing capture, suggesting that this effect is in fact a fundamental limitation of mechanical stimulation itself [104]. In that study,

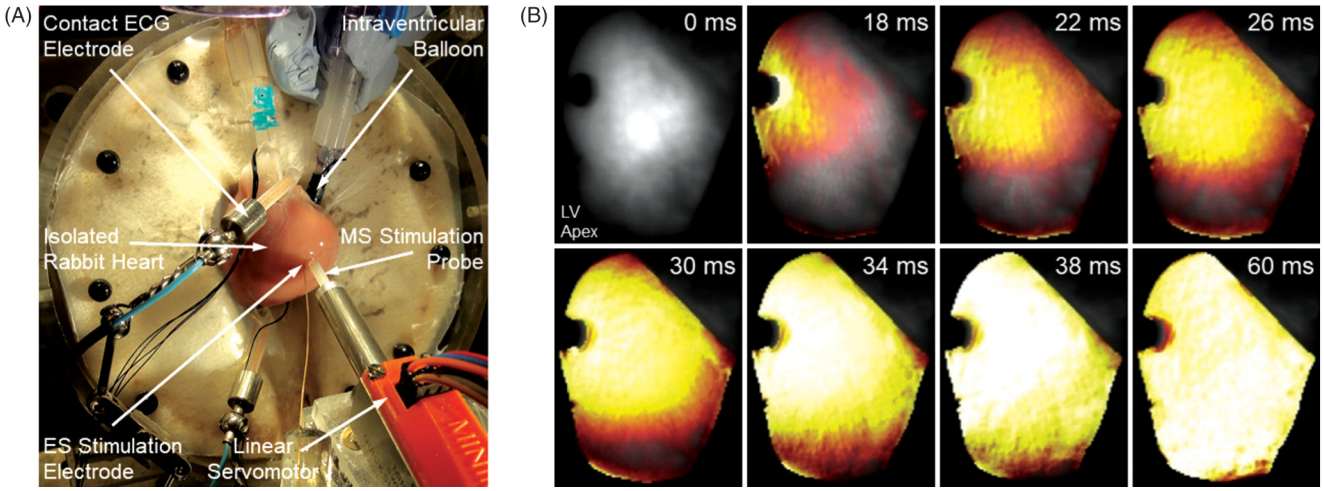

FIGURE 39.14 **Local epicardial mechanical pacing and left ventricular excitation visualized by optical mapping.** (A) Experimental setup, showing an instrumented isolated rabbit heart (ES indicates electrical stimulation electrode and MS indicates mechanical stimulation probe). (B) Representative voltage optical mapping recording of mechanically induced focal left ventricular excitation during mechanical pacing. *Reproduced with permission from Quinn and Kohl [104].*

it was found that repetitive local mechanical stimulation of the left ventricular epicardium causes repeated focal excitation (Fig. 39.14), but that 1:1 capture is reversibly lost after a finite number of stimulations in a stimulation rate dependent manner, even though the tissue remains electrically excitable (Fig. 39.15). While the mechanism for the loss of capture with repetitive mechanical stimulation was not investigated in that study, it was speculated that mechanical stimulation and electrical stimulation are limited by different types of (mechanical and/or electrical) 'refractoriness.' This concept is supported by a study of repetitive local stimulation of left ventricular epicardium in open-chest anesthetized dogs that demonstrated a decrease in the effective refractory period with electrical, but not mechanical stimulation [105]. In another dog study, in which a mechanical stimulation was applied every 8–12 sinus beats, mechanical stimulation during the relative refractory period (established by electrical stimulation) resulted in excitation only with every second or third mechanical stimulation [106]. Finally, in a study using transient inflation of an intraventricular balloon as the means of mechanical stimulation, repeat inflations were effective only after periods of rest (up to 1 minute for full recovery of mechanically induced excitation) [107]. Overall, these studies suggest that mechanical simulation indeed involves a pool of mediator(s) that is different from established mechanisms of electrical refractoriness.

Potential mechanisms for an MEC adaptation period, during which there is a temporary reduction in the potential for mechanically induced excitation that returns after a period of normal sinus rhythm, might include effects of mechanical stimulation on: (1) tissue mechanical properties (passive or viscoelastic); (2) SAC_{NS} (or other ion channel activity); (3) ionic distributions and/or availability; (4) intracellular domains (such as sarcoplasmic reticulum or mitochondria); (5) second messenger systems depletion or activation that influence the earlier; or (6) other unknown factors necessary for mechanically induced excitation.

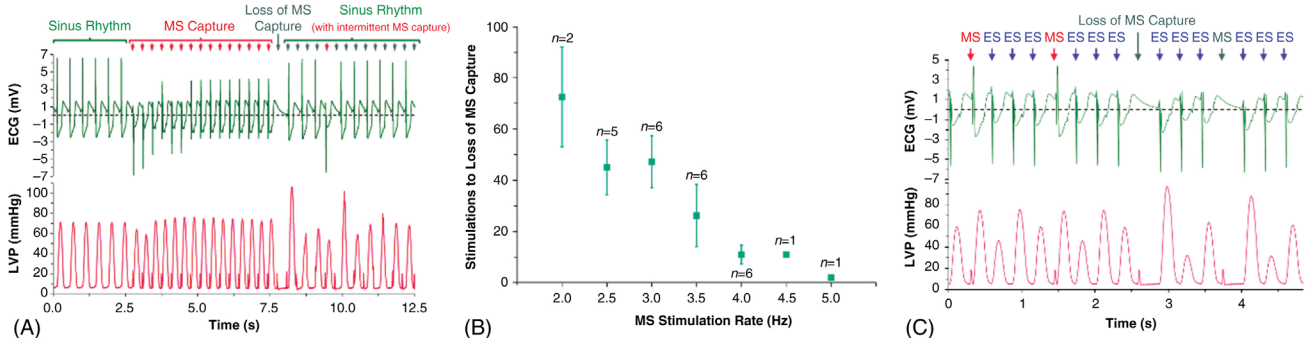

FIGURE 39.15 **Loss of mechanical pacing capture.** (A) Electrocardiogram (ECG) and left ventricular pressure (LVP) recordings during sinus rhythm, followed by a train of mechanical stimulations (MS) during which loss of 1:1 capture occurs, resulting in a return to sinus rhythm with intermittent MS capture. (B) Effect of overdrive pacing rate by MS on the number of stimulations to loss of 1:1 capture. (C) ECG and LVP recordings during a train of 1:3 MS:electrical stimulations (ES) during which loss of MS capture occurs, while ES capture is maintained. *Reproduced with permission from Quinn and Kohl [104].*

There is some evidence supporting these potential mechanisms for a loss of mechanical pacing capture. In terms of potential effects on myocardial mechanics, during mechanical testing of contracting whole hearts, a reversible decrease of muscle stiffness is seen between the first and subsequent deformation cycles, which recovers after ~30 seconds of rest [108]. This viscoelastic effect could contribute to an MEC adaptation period, further supported by the observed stimulation rate-dependent decrease in the number of mechanical stimulations before a loss of pacing capture.

The concept that SAC_{NS} show "mechanical refractoriness" is supported by the observation that repeated mechanical stimulation causes a reduction in measured SAC_{NS} current in acutely isolated embryonic chick heart cells unless stimulations are spaced minutes apart [109]. Similarly, mechanically induced current of Piezo channels has been shown to decrease with repetitive stimulation in HEK293t cells expressing the channels, and this leads to a frequency dependent loss of mechanically induced excitation of sensory dorsal root ganglion neurons [110]. This apparent use-dependent decrease in mechanically activated currents could be partly responsible for a rate-dependent decrease in the number of mechanical stimulations to a loss of pacing capture.

The potential for mechanical effects on ionic concentrations, especially via modulation of sub-cellular compartments, is supported by the evidence for direct mechanical effects on intracellular calcium handling in cardiac cells [111]. These effects include an acute stretch-induced increases in localized sarcoplasmic reticulum calcium-release events ("calcium sparks") in ventricular myocytes (which reduces sarcoplasmic reticulum calcium levels) [112] and calcium release from mitochondria (whose intra-organelle calcium concentrations may also be affected) [113]. If alterations in calcium handling (such as stretch-induced calcium-release) are involved in mechanically induced excitation, then a depletion in sarcoplasmic reticulum calcium stores, or of a mechanically releasable sub-pool of calcium, could affect the efficacy of mechanical stimulation. Moreover, an increase in calcium sparks with stretch is thought to result either from direct mechanical stimulation of ryanodine receptor channels [112], or via effects mediated by reactive oxygen species [114]. Both mechanisms could be affected by the frequency of cyclic mechanical stimulation, which could explain the stimulation rate-dependent decrease in the number of stimulations before a loss of pacing capture.

Ongoing studies in rabbit isolated hearts have been investigating the potential mechanisms for a loss of capture with mechanical pacing [115]. Thus far it has been shown that pharmacologically induced changes in active or passive tissue stiffness do not alter pacing sustainability, but that there is a continuously increasing delay between mechanical stimulation and excitation with each successive mechanically paced beat, suggesting that run-down of SAC_{NS} current may be responsible of the loss of capture during mechanical pacing. Further, it has been shown that the time for full recovery of mechanical pacing capture is ~1 minute, with a continuous decrease in the number of captured beats when recovery interval is further reduced, and that sub-threshold mechanical stimulation prior to mechanical pacing reduces the subsequent number of captured beats. Finally, in those studies global ischemia causes a progressive reduction in the number of captured beats, with complete loss of capture occurring after ~15 minutes of ischemia.

39.4.2 Adverse side effects

With mechanical stimulation there is the potential for the induction of cellular and/or tissue damage, which could occur because of mechanical, and in the case of HIFU-based pacing, thermal effects. In terms of HIFU-induced thermal effects, the elevation of tissue temperature to necrosis-inducing levels is unlikely, as HIFU is delivered in relatively short pulses or short-bursts, and coronary perfusion should quickly equilibrate any local temperature rise before application of the next excitation pulse. That said, if stimulation energy level is kept below the FDA guidelines (720 mW/cm^2 in the case of the heart, the parameter given for ultrasound imaging), this should avoid tissue necrosis. Mechanical stimulation, if too intense, also has been shown to cause tissue damage whether by HIFU [66,73–77] or direct mechanical interaction [33,104,116], so stimulation energy levels must again be carefully considered. In terms of direct myocardial stimulation, it has been shown in isolated guinea pig hearts that a pre-impact kinetic energy greater than ~3 mJ results in measurable cellular damage [116]. For HIFU stimulation, the recommended mechanical indicator (which is proportional to the negative peak instantaneous pressure amplitude) should be kept below 1.9, so the inertial cavitation that leads to generation of free radicals can be ruled out. This creates a challenge however, as the acoustic energy at the target must be high enough to reliably cause excitation, but not high enough to result in excessive radiation pressure or cavitation at the stimulation site or in other tissues located along the acoustic beam path. For clinical use, in order to guarantee safe exposure levels at the target tissue, monitoring may be required (e.g., cavitation detection).

The other major concern for cardiac mechanical stimulation is the potential for the induction of sustained (and potentially lethal) arrhythmias [117]. Much like for electrical stimulation or defibrillation [118], a vulnerable window exists during the ECG T-wave in which mechanically induced excitation can be the trigger for ventricular fibrillation (Fig. 39.16) [119]. In the whole heart during electrical systole, membrane potential across the ventricular myocardium is spatially non-uniform. As a result, the timing of a mechanical stimulus relative to the underlying cellular action potential at any

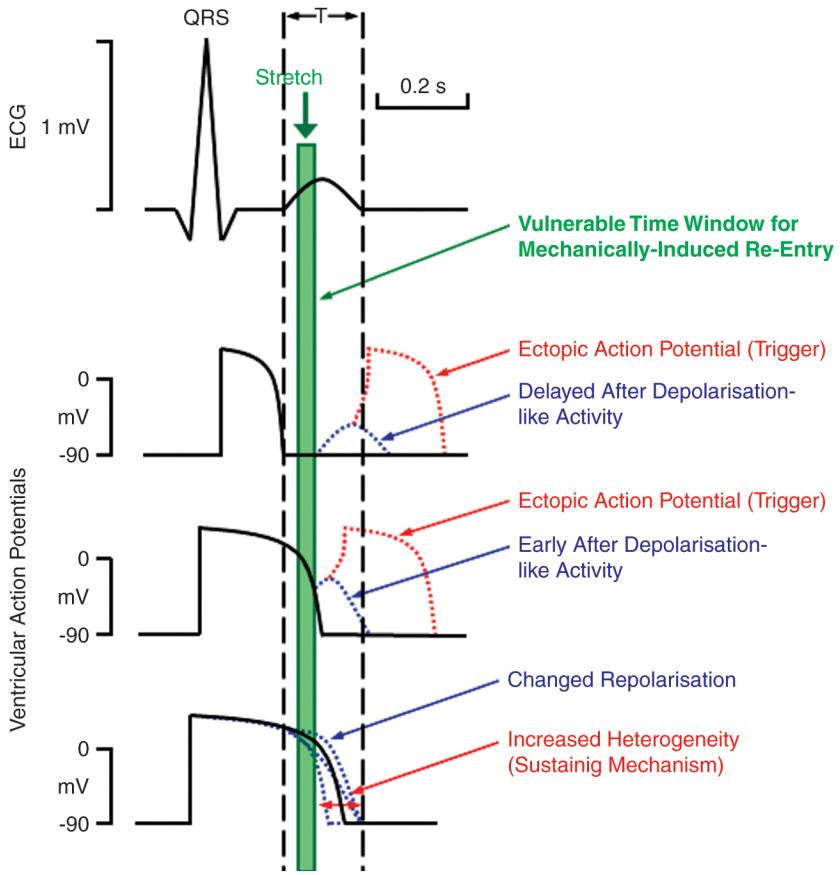

FIGURE 39.16 **Vulnerable window for mechanically induced ventricular fibrillation.** Effects of mechanical stimulation during the ECG T wave *(green bar)* in the whole heart, showing regionally varying response depending on the local phase of the action potential. *Adapted with permission from Kohl et al. [119].*

location will vary. While the ventricular activation wave-front is steep and fast (resulting in a narrow ECG QRS complex and preventing regionally differing responses to mechanical stimulation), repolarization is a more graded process (broader and lower ECG T-wave). As such, mechanical stimulation may give rise to delayed (in cells that have regained excitability) or early (in cells that are repolarizing) after-depolarization-like events. If supra-threshold, these depolarizations can cause ectopic foci, potentially providing a trigger for arrhythmogenesis. Stimulation of cells at more positive membrane potentials may affect the time-course of repolarization, increasing electrophysiological heterogeneity in affected areas of the myocardium, which could contribute to the formation of an arrhythmia-sustaining substrate. The plausibility of this concept has been supported by computational modelling [120,121], and in the clinical and experimental setting of mechanical pacing, while rare, ventricular tachyarrhythmias have been reported to occur with precordial percussion [53], HIFU [93] (Fig. 39.17A), direct epicardial impact [33] Fig. 39.17B, and chest compressions [60,61] (Fig. 39.10B). Thus, in applications of mechanical pacing, stimulation relative to any underlying rhythm should be considered.

39.5 Future directions

39.5.1 Further developments

To meet the challenges described earlier and make mechanical pacing a viable clinical therapy, further developments are needed. Firstly, additional safety testing must be performed to determine mechanical stimulation parameters that do not carry a risk of causing sustained arrhythmias or myocardial damage (e.g., HIFU-based pacing experiments in which temperature and cavitation are monitored). At the same time, the conditions and parameters necessary for sustained mechanically induced excitation must be defined, which necessitates experiments to assess contributing factors, such as: (1) the mode, algorithms, and characteristics of energy application; (2) the maximum viable pacing rate in various states (lower rates will be possible in severely bradycardic and asystolic hearts); (3) the utility of multiple (alternating) or specifically targeted pacing sites; and (4) the inclusion of interspersed short pauses (similar to CPR with interspersed breaths) to regain

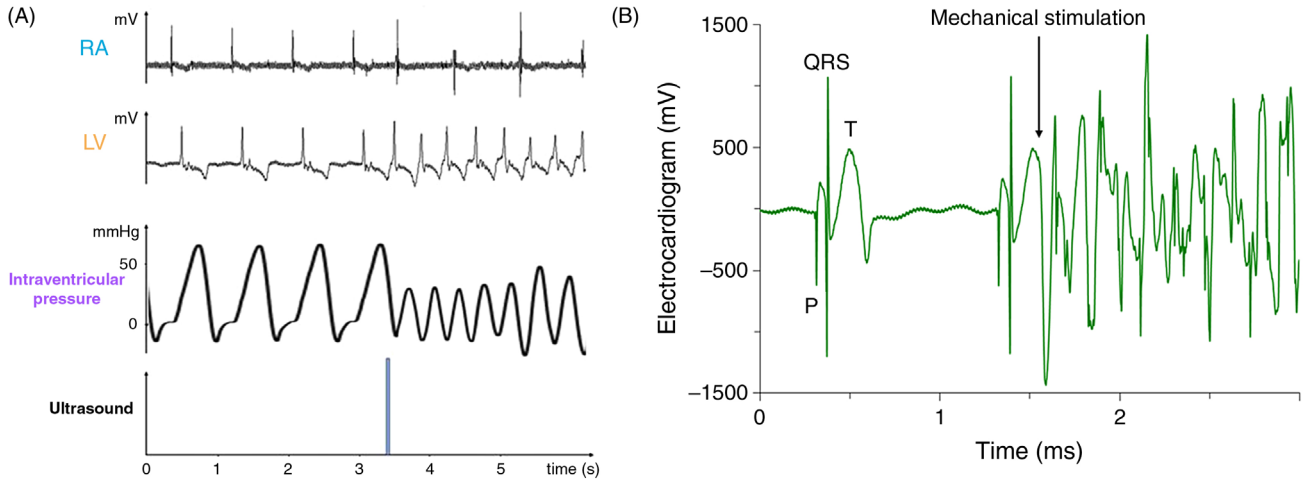

FIGURE 39.17 Mechanically induced ventricular tachyarrhythmias. (A) Electrical (right atrium [RA] and left ventricle [LV]) and hemodynamic recordings of ultrasound-induced ventricular tachycardia in an isolated pig heart after triggering the acoustic pulse to the relative refractory period. *Reproduced with permission from Marquet et al. [93].* (B) Local epicardial mechanical stimulation applied to the left ventricle of an isolated rabbit heart in the early T wave, resulting in instantaneous ventricular fibrillation. *Reproduced with permission from Quinn et al. [126].*

mechanical excitability. Finally, the appropriate method(s) of mechanical stimulation for each application must be defined and optimized, which may require novel devices or technical developments (e.g., for HIFU-based pacing there may be the need for novel transducer geometries or implementation of multiple, regionally dispersed transducers, both of which may be achieved by the use of novel stretchable ultrasound technology [122]).

39.5.2 Potential applications

If the conditions and suitable devices for sustained extracorporeal mechanical pacing can be developed, there is the potential for multiple clinical applications of this technique. As already discussed, it may be a life-saving intervention as a means of temporary pacing and a bridge to instrumentation-based pacing approaches for in- or out-of-hospital emergency situations where patients are suffering from acute bradycardia or asystole. In the case of HIFU, where the ultrasound beam can be focused on particular locations of the heart, this could be extended to include region-specific pacing, such that the atria might be paced during sinus node dysfunction, the ventricles during atrioventricular block, or both the atria and ventricles to restore atrioventricular synchronization in patients needing hemodynamic support. In fact, while the *2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science* from the International Liaison Committee on Resuscitation states that: "Percussion pacing is not recommended in cardiac arrest in general", they do recommend that it: "may be considered in hemodynamically unstable bradyarrhythmia until an electric pacemaker is available" [123]. In the context of clinical electrophysiology, mechanical pacing may be useful for non-invasively terminating existing tachyarrhythmias (such as with precordial thump [124]) or for examining their inducibility. In addition, it may be a valuable tool for determining the patient-specific utility of cardiac pacing in certain disease states and for testing optimal pacing configurations before implantation, including single versus dual chamber versus multi-site pacing, atrioventricular, interventricular, and intraventricular delays, and optimal pacing sites, especially in the context of biventricular pacing ("resynchronization therapy").

39.6 Conclusions

Mechanical pacing has great potential as a rapidly available, non-invasive method for establishing extracorporeal control of cardiac rhythm. Through a long history of clinical and experimental studies, it has been shown to be generally safe and well-tolerated and applied by simple, readily available means or through novel devices. Yet, while it is clear that mechanical stimulation can cause ectopic excitation of the heart, the conditions for sustained pacing remain to be elucidated. With further technological developments and testing of the safety and efficacy of mechanical pacing, this technique has the potential to be a powerful treatment and diagnostic tool for emergency medicine and cardiac electrophysiology applications.

Acknowledgments

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