INNOVATIVE TECHNIQUES

RESEARCH ARTICLE

Anodal Stimulation: from Cell to Clinical Practice

HERMINE R. POGHOSYAN, MD, SERGEI J. BARSAMIAN, MD, ARMAN B. DANOPYAN, MD and SMBAT V. JAMALYAN, MD

Malatia Medical Center, Yerevan, Armenia

ABSTRACT. Anodal stimulation has been an area of active research for decades. Understanding the mechanism and properties of anodal stimulation is important for clinical work-up of cardiac resynchronization therapy (CRT) patients. Anodal capture usually occurs with high output in conventional bipolar endocardial right ventricular (RV) pacing, and in the pseudo-bipolar left ventricular (LV) to RV configuration of biventricular pacing, when the tip electrode of the LV lead is the cathode and the proximal ring electrode of the bipolar RV lead is the anode for LV pacing.

KEYWORDS. anodal stimulation, cardiac resynchronization therapy non-responders, cardiac resynchronization therapy patient, left ventricular electrode.

Anodal stimulation at cellular level

The cellular mechanisms of anodal stimulation are important for understanding the usefulness and challenges of this type of pacing. The heart muscle can be excited by either cathodal or anodal stimulation. The anodal excitation phenomenon was first described by Cranefield et al1 in the late 1950s. According to Hoffman and Cranefield,2 cathodal stimulation of the heart can be explained by direct depolarization of the cells in the area under the electrode. Sepulveda et al3 found strong depolarization under the unipolar cathodal electrode, and adjacent hyperpolarization near the electrode along the direction of the fiber.

Later, Dekker4 demonstrated that the myocardium could also be excited by anodal stimulation and identified two mechanisms of excitation in the heart: “make” and “break.”1,2 Make excitation occurs after the stimulus is turned on, and break excitation occurs when the stimulus is turned off, stimulating a refractory tissue. Both of these mechanisms occur in cathodal and anodal stimulation. Therefore, there are four possible excitations: cathode make and break, anode make and break.4 An anodal pulse applied during the relative refractory period repolarizes the heart to a level that depends on the strength of the stimulus and results in hyperpolarization of the underlying tissue, so its ability to trigger an action potential is paradoxical.5 Development of a bidomain model of cardiac tissue facilitated the theoretical understanding of electrical cardiac electrical excitation. Four mechanisms of excitation, as described by Kandel and Roth6 using the bidomain model are presented in Figure 1.

The bidomain model is a two- or three-dimensional cable model that accounts for the anisotropy of the intracellular and extracellular spaces.5 Unequal anisotropy in the two domains leads to marked inhomogeneities in the induced membrane potential around the stimulating electrode.7

As shown in Figure 1, during anodal stimulation a dog-bone-shaped region of the tissue underlying the stimulating electrode becomes hyperpolarized, whereas regions lying in the convexity of the dog bone become depolarized and are referred to as “virtual cathodes.” It is proposed that, during anodal stimulation, the excitation wavefront starts from these virtual cathodes.6–8

All these aspects have clinical implications. Break-stimulation is not useful in clinical practice as the impulse has to be delivered at a period during which the myocardium is refractory, and it generally requires a higher current density, with a potential of myocardial damage and localized hydrolysis around the physical electrode.5 There are some concerns that anodal pulses, because of a lower threshold in the refractory period, imply a higher arrhythmic risk than cathodal pulses. The absolute refractory period is typically shorter in anodal stimulation. So, if a stimulus falls in the vulnerable period of a spontaneous cycle, the risk of triggering a
Pacing configuration, myocardial vulnerability and anodal stimulation

In unipolar configuration, the electrode stimulating the cardiac chamber typically is the cathode of the pacing circuit. It must be in direct contact with the myocardium. In bipolar configuration, both the anode and the cathode are in contact with the heart.

Acute animal experiments and clinical experience indicate that ventricular vulnerability to fibrillation or multiple premature contractions is greater during bipolar or anodal stimulation than with unipolar cathodal stimulation (with electrodes of equal cathodal and anodal surface area), because the anodal and bipolar absolute refractory periods are shorter, enabling easier excitation in the vulnerable period. The same study shows that to decrease the risk the anodal surface area should be five to seven times the cathodal surface area, or the anode should be removed from the ventricle, especially for temporary pacing in circumstances of high vulnerability to arrhythmias.

Cardiac resynchronization therapy (CRT) generally utilizes the bipolar lead for right ventricular (RV) pacing and either a unipolar or a bipolar lead for left ventricular (LV) pacing. There are two possible bipolar configurations for LV CRT: true bipolar and extended bipolar. These configurations are illustrated schematically in Figure 2.

Using the RV ring as the anode is the only available configuration with unipolar LV leads. It is also common when configurations are serially changed to reduce phrenic stimulation or LV pacing threshold. A recently published study shows that maximum safety with regard to phrenic stimulation is achieved in the LV tip to LV ring configuration, but in some cases, the LV ring to RV ring/coil configuration can be advantageous.

High-amplitude LV stimulation with the RV ring serving as the anode (LV-only pacing) may result in local anodal capture at the RV ring site. High LV output probably works via enlargement of the myocardial capture area beyond the site of the conduction block, creating a larger virtual electrode. A larger virtual electrode may be of particular importance for RV anodal capture and in the pacing of diseased myocardium, but it may be complicated by phrenic stimulation and rapid battery depletion.

Anodal stimulation may occur during LV-only pacing or during biventricular (BiV) pacing when it creates a setting of triple-site pacing (RV tip, LV tip, and RV ring are all capturing simultaneously).

Anodal stimulation is absent in configurations where the LV electrode is combined with the RV coil electrode as the anodal electrode, because of the surface area of this electrode (around 500 mm²). The current density in this case is too low to result in anodal capture.

Figure 1: A schematic illustration of the four mechanisms of excitation. Fiber orientation is along the horizontal axis and the electrode is indicated by the black dot. D stands for depolarization and H for hyperpolarization. Reproduced with permission (Kandel SM, Roth BJ. The strength–interval curve in cardiac tissue. Comput Math Methods Med 2013; doi: 10.1155/2013/134163).

Figure 2: Schematic illustration of the extended bipolar configurations.

---

**Table:**

<table>
<thead>
<tr>
<th>Configuration</th>
<th>RV Ring</th>
<th>LV Tip</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV coil</td>
<td>LV tip</td>
<td>LV tip</td>
</tr>
<tr>
<td>LV tip to RV coil</td>
<td>RV true bipolar lead</td>
<td>Capture from the cathode (LV tip)</td>
</tr>
<tr>
<td>RV integrated bipolar lead</td>
<td>LV tip</td>
<td>RV true bipolar lead</td>
</tr>
<tr>
<td>Capture from the anode (RV ring) and cathode (LV tip) simultaneously</td>
<td>Anodal stimulation</td>
<td></td>
</tr>
</tbody>
</table>
problem may be more frequent in children, given the small size of their hearts.\textsuperscript{13}

**Anodal stimulation and lead type**

A prospective multicenter study has suggested that anodal stimulation is more common in dedicated than integrated bipolar defibrillation leads due to smaller lead surface area resulting in higher current density causing increased risk of surrounding myocardial depolarization.\textsuperscript{14}

**Effects of anodal stimulation on myocardial contractility and echocardiography**

Nevertheless, there are some experimental studies suggesting that anodal stimulation increases the conduction velocity, which may lead to higher contractility and thus increase the mechanical response produced by anodal stimulation. The mechanism of these changes is not fully understood, but may be explained by calcium ionic currents.\textsuperscript{15} Some small trials have also demonstrated acute beneficial effects of anodal stimulation on cardiac output and LV function.\textsuperscript{16,17} Another study showed that a minority of patients with CRT may have worsening of LV function acutely with anodal stimulation, although there was no change in most patients.\textsuperscript{18}

**Effects of anodal stimulation on electrocardiogram**

Factors that determine the final QRS morphology in patients with CRT are:

1. location of the right and LV leads,
2. the programmed A-V and V-V intervals,
3. intrinsic A-V conduction,
4. the presence or absence of anodal capture.

A recently published study on the incidence of anodal stimulation among CRT patients has shown that during LV-only pacing in the LV tip to RV ring configuration, anodal stimulation is present in 78% of patients, and it can be recognized by 12-lead ECG in only 41% of those patients.\textsuperscript{18}

The changes on ECG were often subtle: triple-site pacing occurs from three different foci and this may result in improved resynchronization, as anodal stimulation results in a narrower QRS. In this case the QRS duration may decrease by 10–20 ms and QRS amplitude of leads I and aVL may increase.\textsuperscript{19}

The data of Sweeney et al.\textsuperscript{20} suggest that a marked increase in R-wave amplitude (compared with baseline) in lead V1 favors a positive response to CRT. The true configuration of lead V1 can be easily evaluated during BiV VVI pacing at rates faster than the spontaneous rate. If the RV lead is in the apex, the device is in LV to RV mode and there is no tall R wave in V1, RV anodal stimulation must be ruled out.\textsuperscript{21}

If BiV pacing looks like RV pacing, only anodal stimulation must be ruled out. In this case, it is very helpful to compare QRS in BiV pacing with low LV output and with high LV output. High-amplitude LV stimulation with the RV ring serving as anode may result in local anodal capture at the RV ring site. So in low output LV pacing we may see narrow QRS complexes; only in high output LV pacing does it look like RV pacing (Figure 3).

**Anodal stimulation and CRT programming challenges**

Anodal stimulation may negate any benefit of V-V optimization because anodal capture reduces the V-V interval to zero.\textsuperscript{22} A small study suggested that anodal stimulation could be under-recognized because of non-response to CRT.\textsuperscript{23} However, the editorial conclusion for the aforementioned article was that “this is an interesting hypothesis, but not a convincing conclusion.”\textsuperscript{24}

**Figure 3:** QRS changes during left ventricular high output pacing because of anodal stimulation.
Common misinterpretation of the loss of anodal stimulation as a loss of capture during LV lead threshold testing may lead to inappropriate programming of high outputs of LV pacing. On the other hand, if anodal RV capture is mistaken for LV capture, the LV pacing output may be programmed to a subthreshold value, resulting in a loss of resynchronization. It is much more common for the RV anode to be represented by the ring electrode (true bipolar pacing), which has a small surface area and high current density) and may be in direct contact with endocardium rather than the RV anode being the defibrillation coil (integrated-bipolar pacing), which has a large surface area and low current density.

Anodal stimulation and manufacturers

Despite the absence of studies evaluating the incidence of anodal stimulation in different manufacturers, existing data suggest that anodal capture is extremely rare in Medtronic and Guidant implantable cardioverter-defibrillators (ICDs), which use integrated bipolar pacing. St. Jude Medical ICDs use true bipolar pacing if the LV lead is unipolar, which, combined with a true bipolar RV lead, may sometimes result in anodal capture.

However, when a true bipolar ICD lead (e.g. Medtronic) is combined with a device that is usually equipped with integrated bipolar leads (e.g. Guidant), the LV tip to RV coil pacing configuration leads to stimulation between the LV tip and RV ring with possible anodal capture. Anodal RV capture can easily be prevented by the use of bipolar coronary sinus (CS) leads (e.g. Medtronic 4194). In this lead, the ring electrode has a surface area of 38 mm², but, despite this large surface area, the stimulation threshold is lower when the coil electrode of an ICD lead with a surface area of approximately 500 mm² is used as the anodal electrode.

In recently introduced bipolar CS leads the proximal electrode has a surface area approximately equal to the surface area of the distal electrode (e.g. Guidant Easytrak 2, Medtronic 4196). These leads are far from ideal when used in a bipolar configuration, because the small surface area of the proximal electrode gives a rise in lead impedance without an increase in current density. The idea behind the lead is that the stimulating electrode can be switched from distal to proximal in a unipolar configuration, in which the coil of the ICD lead is used as the anodal electrode.

Quadrupolar CS leads increase the number of pacing vectors, providing more programming flexibility to avoid phrenic nerve stimulation and high pacing thresholds.

Clinical implications

Anodal stimulation is found only in the setting of relatively high outputs, only with bipolar RV leads, and usually in the LV tip to RV ring configuration.

If BiV pacing is on and the electrocardiogram resembles conventional RV pacing, anodal stimulation should be suspected.

Prior to V-V interval optimization, the pacing lead configuration should be considered to exclude possible anodal capture, which reduces the V-V interval to zero. Careful analysis of the 12-lead ECG during RV, LV, and BiV pacing is crucial. An effective way to avoid anodal stimulation is programming the device in unipolar configuration using the can of the device as the anode in absence of pectoral muscle stimulation.

Summary

The advantages and challenges of anodal stimulation need to be evaluated in a prospective, crossover study. It is very possible that exciting times lie ahead.

References

15. Thakral A, Stein LH, Shenel M, Gramatikov B, Thakov N. Effects of anodal vs. cathodal pacing on the mechanical stimulation.