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Review

Intracoronary acetylcholine application as a possible probe inducing J waves in patients with early repolarization syndrome

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ABSTRACT

Acetylcholine is widely used for a diagnostic provocation test of coronary spasm in patients with vasospastic angina. Acetylcholine usually induces coronary vasodilatation mediated by muscarinic receptor activation, but sometimes it evokes vasoconstriction of coronary arteries where the endothelium is damaged. Early repolarization syndrome is characterized by a J wave observed at the end of the QRS complex in a surface electrocardiogram. The J wave is attributed to the transmural voltage gradient at the early repolarization phase across the ventricular wall, which stems mainly from prominent transient outward current in the epicardium, but not in the endocardium. Transient high-dose application of acetylcholine into the epicardial coronary arteries provides a unique opportunity to augment net outward current, selectively, in the ventricular epicardium and unmask the J wave, irrespective of the cardiac ischemia based on coronary spasm. Acetylcholine augments cardiac membrane potassium conductance by enhancing acetylcholine-activated potassium current directly and by activating adenosine triphosphate-sensitive potassium current, in addition to the reduced sodium and calcium currents in the setting of severe ischemia due to vasospasm. However, the role of acetylcholine as an arrhythmogenic probe of the J wave induction in patients with suspected early repolarization syndrome warrants future prospective study.

Contents

1. Introduction

In the last century, intracoronary application of acetylcholine (ACh) was established as a diagnostic provocation test of coronary

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spasm in patients with suspected vasospastic angina. Because the effects of ACh is short-lived, this provocation test can evaluate the direct effects of high-dose ACh on vasomotion in the epicardial coronary arteries. Vasospasm is considered to be the dysregulation of endothelium controlling vasomotion, inappropriate hypercontractility of vascular smooth muscle, or both [1]. ACh yields endothelium-dependent muscarinic vasodilation in normal coronary arteries, whereas it induces vasoconstriction in coronary arteries with endothelial injury [2]. Since autonomic regulation involves arrhythmogenesis as well as coronary vasomotor tonus, intracoronary high-dose application of short-lived ACh may have a key role, not only in the diagnostic provocation test of coronary vasospasm, but also in the arrhythmogenesis by cholinergic electrophysiological actions, irrespective of the association with severe cardiac ischemia due to coronary spasm.

2. Discussion

2.1. ACh and coronary spasm provocation test

ACh, a neurotransmitter of the parasympathetic nervous system, is inactivated quickly by circulating cholinesterase, and is effective for only a very short period when applied by intracoronary injection. Vasomotor function is regulated by the balance between the endothelium-derived contracting factors (thromboxane A_2, leukotrienes, and others) and the relaxing factor of nitric oxide (NO). ACh disrupts the intrinsic balance of endothelium-derived opposing factors leading to the focal or diffuse coronary spasm at the site, releasing insufficient NO [3]. This property is utilized widely in coronary angiography to evoke coronary spasm for diagnosis of vasospastic angina.

Although the spasm provocation test using ACh is regarded as a safe and reliable technique to diagnose vasospastic angina, arrhythmogenic complications are not unusual. Consequently, the Japanese Circulation Society guideline recommends temporary pacemaker lead insertion during ACh application to reverse transient bradycardia and atrioventricular block based on parasympathetic activation [4]. Paroxysmal atrial fibrillation (AF) is also ascribed to the cholinergic effects of ACh on the atria, where ACh-activated potassium (K^+) channels are abundant. The activation of ACh-activated K^+ current ($I_{K\text{-}ACh}$) reduces atrial refractoriness heterogeneously, which underlies focal ectopic activities triggering AF and multiple reentries sustaining AF [5,6]. Sueda and Kohno have reported more serious complications of this provocation test [7]. They concluded that ventricular tachycardia and/or fibrillation (VT/VF), observed during the intracoronary application of ACh, occurred more frequently than with the intracoronary injection of ergonovine, and that VT/VF occurred more frequently in Asian patients than in Western patients undergoing the ACh application test. Although spasm-induced myocardial ischemia is the main underlying cause of serious complications, such as cardiogenic shock and severe hypotension associated with VT/VF, the exact etiology of the VT/VF observed in the ACh provocation test remains to be determined.

2.2. Cardiac ischemia and early repolarization syndrome (ERS)

ACh was originally applied for the diagnostic provocation test of coronary spasm in patients with suspected vasospastic angina [2]. Coronary vasospasm results in severe cardiac ischemia by profound reduction of major epicardial coronary flow and evident ST segment elevation on a surface electrocardiogram (ECG). The relationship between ERS and vasospastic angina has been drawing increasing attention, since the J wave is sometimes observed immediately before the onset of VT/VF in patients with vasospastic angina and acute myocardial infarction (AMI) [8–12]. Acute cardiac ischemia is accompanied by marked reduction of oxygen supply, tissue acidosis, accumulation of ischemic metabolites, and subsequent electrophysiological and electrocardiographic derangements [13]. Cardiac repolarization is accelerated by the sum of reduced inward sodium (Na^+) and calcium (Ca^{2+}) currents (I_{Na} and I_{Ca}) and augmented various outward K^+ currents, which is heterogeneous, because of the differential sensitivity to ischemia between the epicardium and endocardium [14,15].

VT/VF, observed in ERS during ischemic events, are considered to be because of regionally different ischemic sensitivity, leading to phase 2 reentry. When considering that transient outward current (I_{to}) is a major ionic current responsible for J wave formation, in 1988, Litovsky and Antzelevitch reported that epicardial I_{to} is prominent relative to endocardial I_{to} [16]. Thereafter, the ventricular wall was recognized as being heterogeneous with respect to the I_{to} channel expression, density, and I_{to}-mediated epicardial phase 1 magnitude [17–19]. Moreover, epicardial I_{to} is suspected to be more sensitive to ischemia compared with the endocardial I_{to}. In 1993, Lukas and Antzelevitch investigated this regionally different sensitivity of I_{to} to ischemia in canine hearts [14]. They demonstrated that the action potential (AP) plateau was abolished in the epicardium but not abolished in the endocardium by simulated ischemia (hypoxic and acidic conditions with high K^+ concentration) and that 4-aminopiridine restored the epicardial AP plateau. I_{to} is sensitive to 4-aminopiridine, and is a major time-dependent, voltage-sensitive current responsible for early repolarization. Conversely, there are ligand-gated, time-independent outward K^+ currents. Intracellular adenosine triphosphate (ATP) has a ligand action to inhibit ATP-sensitive K^+ channel current ($I_{K\text{-}ATP}$). $I_{K\text{-}ATP}$ is activated by severe ischemia associated with intracellular ATP depletion, leading to AP shortening and extracellular K^+ accumulation [20]. Pharmacological modulation of $I_{K\text{-}ATP}$ affects the canine epicardial, but not the endocardial, AP repolarization, development of phase 2 reentry, and lethal ventricular arrhythmia, i.e., $I_{K\text{-}ATP}$ activation by pinacidil promotes, whereas $I_{K\text{-}ATP}$ inhibition by glybenclamide suppresses, these electrophysiological findings in canine ventricular tissues. These results indicate that $I_{K\text{-}ATP}$ shows regionally different sensitivity to ischemia and plays a crucial role in the ischemic J wave formation and subsequent occurrence of VT/VF [21]. Identification of patients at risk of ischemic VT/VF is important. Arrhythmogenic vulnerability in the setting of AMI may be associated with a genetic predisposition, leading to the heterogeneous excitability, refractoriness, and conduction, which are based on depolarization and/or repolarization abnormalities [22].

2.3. J wave and ERS

ERS is characterized by J point elevation on surface ECGs, and the J wave is characterized by dynamic morphological changes that show a hump, notch, or slur at the end of the QRS complex on surface ECGs. Global prevalence of the J wave in the general population varies widely from 0.9% to 24.8% [23], which depends on the ethnicity, age, gender, and the diagnostic criteria of the J wave itself. ERS was formerly considered a normal benign repolarization variant, but the cumulative evidence, since 2008, indicates that ERS contains a possible risk of lethal VT/VF and sudden cardiac death (SCD) [24].

The Shanghai score system for diagnosis of ERS was proposed by the expert consensus conference [25]. Based on this proposal, patients with ERS, showing dynamic changes of J point elevation, followed by descending ST segment, observed in inferior leads, associated with short-coupled premature ventricular beats (PVBs), are considered to be in a high-risk group. Patients showing bradycardia-dependent J waves also have a poor prognosis,

whereas those with tachycardia-dependent J waves showed no SCD [26]. The exact mechanisms of such phenotypic ECG manifestations of the J wave, leading to poor prognosis, are explained by the electrocardiologic differential theory, i.e., bradycardia induces full recovery of I_{to} from the preceding AP, leading to an accentuated phase 1 notch and a delayed AP dome in the epicardium. A distinct phase 1 notch in the epicardial AP is reflected by high amplitude J waves. Delayed appearance of the epicardial AP dome forms an inward transmural voltage gradient in the late repolarization phase, which causes a descending ST segment and an inverted T wave. A prognostic difference of ERS in inferolateral comparison is also noted, i.e., the inferior ERS shows a poor prognosis relative to the lateral ERS [25]. This is explained by the fact that inferior I_{to} density is greater than lateral I_{to} density [27].

2.4. Brugada syndrome and ERS

Brugada syndrome (BrS) was first reported in 1992 by Brugada and Brugada [28] in a multicenter report. Electrocardiographic manifestations of BrS were described originally as right bundle branch block and persistent ST segment elevation. However, these characteristic features are interpreted today as an early repolarization pattern, observed particularly in the anterior right ventricular outflow tract region [25]. Moreover, patients with BrS, associated with inferolateral early repolarization pattern show a higher risk of VT/VF, indicating that BrS, in addition to inferolateral early repolarization, reflects extensive J wave manifestations, leading to an electrical storm [29–31]. BrS and ERS are related manifestations in a broader spectrum of J wave syndromes, i.e., primary electrical disorders without structural heart diseases [25].

BrS and ERS show common features of inherited channelopathy, pathophysiological mechanisms causing VT/VF, and therapeutic effectiveness of pharmacological and non-pharmacological options. Both syndromes show ischemic ST elevation, male predominance, and evident vagal influences [32]. The magnitude of ST elevation and the occurrence of VT/VF in patients with BrS and ERS are generally dependent on heart rate [33] and frequently observed at night, with a full stomach or when vomiting [34–36]. Vagal dominance in the genesis of VT/VF in these patients is also reported in clinical studies using heart rate variability [37] and other autonomic function tests [38]. These syndromes are associated with mutations or rare variants of genes encoding channel proteins of $I_{K\text{-}ATP}$, I_{Na}, or I_{Ca}, which result in the gain of function in $I_{K\text{-}ATP}$ or the loss of function in I_{Na} and I_{Ca}. With respect to therapeutic options, isoproterenol infusion is emerging as a promising pharmacological intervention. Quinidine and bepridil are effective as conservative pharmacological treatments. Implantable cardioverter-defibrillators (ICDs) should be considered in cases presenting with drug-refractory VT/VF. These pharmacological and non-pharmacological modalities are common therapeutic strategies in treatment of J wave syndromes.

However, there are some differences between the J wave syndromes when comparing the provocation test and long-term prevention of arrhythmic events. Diagnostic tools for BrS are not necessarily helpful in ERS, since BrS is unmasked on surface ECG by using a class Ic antiarrhythmic agent, which is a potent blocker of I_{Na}. In Japan, pilsicainide is an example of a class Ic agent widely used for diagnostic testing for suspected BrS. However, class Ic agents tend to mask J waves in ERS, partly because of the QRS widening based on the ventricular conduction slowing [25]. Therefore, pharmacological probes to evoke persistent J waves have not yet been established. Antiarrhythmic effects of marine-derived ω-3 fatty acids, such as eicosapentaenoic acid (EPA), on ERS are reported in Japan. Hisamatsu et al. investigated the preventive effects of ω-3 fatty acid intake on cardiac death in community-dwelling men, without baseline cardiac diseases, in a prospective study. They concluded that risk of cardiac death associated with ERS might be attenuated by dietary intake of ω-3 fatty acid [39]. Endo et al. also investigated the relationship between serum EPA concentration and ERS in patients with AMI undergoing percutaneous coronary intervention. They demonstrated that J wave appearance and arrhythmic events were more frequent in patients with low serum EPA and suggested that the J wave is linked to low EPA in patients with AMI associated with ischemic VT/VF [40]. However, such favorable effects of EPA on BrS have not yet been reported.

2.5. ACh and the J wave

Screening out small groups of high-risk patients with ERS from the vast majority of those in the low-risk group of ERS and then giving appropriate therapy with an ICD to the limited high-risk patients, is essential to prevent SCD caused by VF/VT. For this purpose, use of pharmacological agents for diagnostic J wave induction is required. Kodama et al. reported a case of aborted SCD presenting with a de novo J wave by a coronary spasm provocation test using ACh [41]. A 51-year-old man experienced a cardiac arrest during a winter full marathon. He underwent by-stander cardiopulmonary resuscitation and he was rescued without the use of an automated external defibrillator (AED). Vasospastic angina was suspected, and no structural heart diseases were found by routine noninvasive cardiac examinations after referral.

During left coronary infusion of ACh, this patient did not complain of chest pain, and coronary angiography demonstrated no spastic findings. The surface ECG demonstrated no discernible ST-T changes but distinct J waves in the inferior leads (Fig. 1). Short-coupled repetitive PVBs (Fig. 1) and the gradual appearance of J waves (Fig. 2) were observed during an increase in ACh dose from 10 to 100 μg. Since there was no evidence of coronary spasm in this case, dose-dependent effects of ACh on surface ECG findings are presumably based on the direct pharmacological actions of ACh, but not mediated by cardiac ischemia. In ambulatory monitoring performed after the ACh application test, nocturnal appearance of the J waves and their disappearance in the early morning were consistent with the cholinergic actions of ACh (Fig. 3). Although no evidence for life-threatening arrhythmia was found, ACh-induced couplet premature ventricular beats (PVBs), as

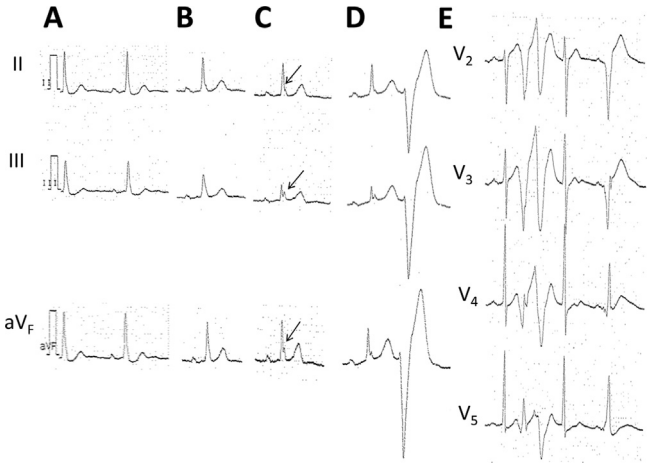

Fig. 1. Electrocardiogram (ECG) recorded before (A) and under coronary spasm provocation test using the following incremental doses of acetylcholine (ACh): 10 μg (B), 30 μg (C), and 100 μg (D). J wave was absent before but was evident in the inferior leads of ECG during ACh administration (arrows). Short-coupled repetitive premature ventricular beats (PVBs) were observed in the precordial leads at the maximum dose of ACh (E). The origin of the triggering PVBs with superior-axis and left-bundle-branch-block morphology is not inconsistent with the area presenting with a J wave [41].

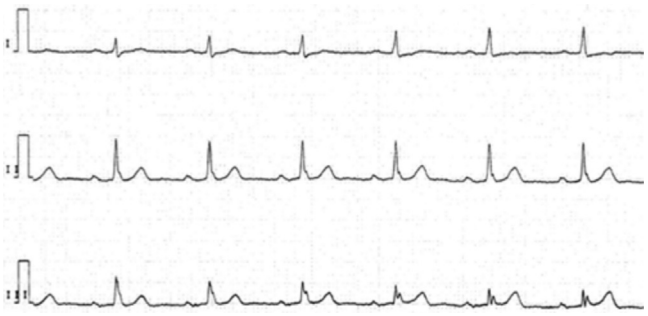

Fig. 2. Electrocardiogram (ECG) during the coronary spasm provocation test using acetylcholine (ACh). A persistent J wave was shown in lead II, whereas gradual fragmentation of the QRS complex and clear J wave formation were observed in lead III under the application of the maximum dose (100 μg) of ACh. The minimal amplitude of the S wave in lead I was not augmented according to the appearance of the J wave in lead III, indicating that this surface ECG does not indicate that a right bundle branch block was caused by ACh.

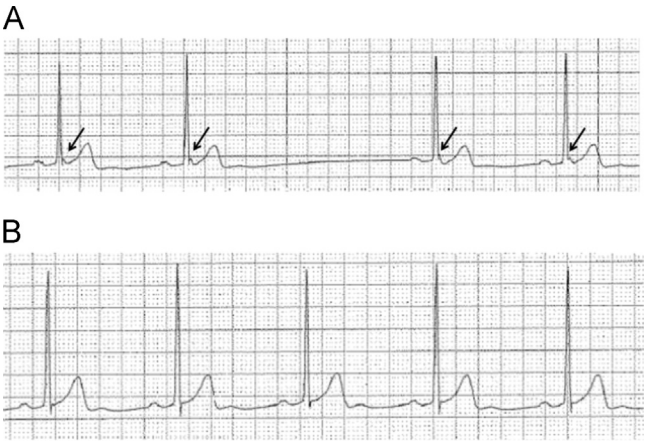

Fig. 3. Ambulatory electrocardiogram monitoring indicates nocturnal appearance of a J wave at the end of the QRS complex (arrows), associated with a transient sinoatrial conduction block recorded at 23:46 pm (A), and disappearance of the J wave in the early morning at 6:55 am (B) at the equivalent baseline heart rate, i.e., minimum RR interval in A is 1240 ms, and basic RR interval in B is 1160 ms.

observed in Fig. 1, are considered as a cause of the aborted SCD in this patient with a resuscitation history.

2.6. Mechanistic consideration

J waves are currently recognized as a surface ECG manifestation of the transmural voltage gradient of epicardial, in contrast to endocardial, ventricular AP at the early repolarization phase (phase 1) [25]. At that moment, the transmural voltage gradient is augmented by a distinct epicardial AP notch, caused by activation of I_{to}. ACh is considered to evoke J waves irrespective of the outcome of the provocation test of coronary vasospasm using ACh.

An example of a positive case of the ACh application test was Sato et al.'s investigation of ischemic J wave dynamics in relation to ST segment changes [42]. They compared the VF occurrence in patients with vasospastic angina presenting with J waves, with those showing no J waves in the baseline ECG. They concluded that J wave appearance is associated with ST elevation and that these ECG findings are a sign of ischemic VF. The ischemic J wave is based on the accelerated epicardial repolarization because of the greater sensitivity of the epicardium to ischemia [14,15]. Different ischemic sensitivity across the ventricular wall is attributed to the preferential activation of epicardial, but not endocardial, $I_{K\text{-}ATP}$ [21]. In addition to the transmural difference, there is also an inferolateral difference, i.e., inferior I_{to} density is greater than lateral I_{to} density [27], which is compatible with the fact that J waves are observed particularly in inferior leads, indicating a high risk of VF in patients with vasospastic angina [12,25,27]. In acute ischemia, inward currents are suppressed, i.e., tissue acidosis inhibits I_{Ca}, and interstitial K^+ accumulation inactivates I_{Na} [13], which also promotes an outward shift in balance of the net transmembrane ionic currents.

Even in a negative provocation test, ACh increases membrane K^+ conductance by enhancing $I_{K\text{-}ACh}$, which is abundant in the atria but is also found in the ventricles. Koumi and Wasserstrom demonstrated that human ventricular $I_{K\text{-}ACh}$ shows channel conductance and kinetics similar to those in human atrial $I_{K\text{-}ACh}$, but that ventricular $I_{K\text{-}ACh}$ (concentration of ACh at half-maximal stimulation (K_D)=0.13 μM) is less sensitive to ACh relative to atrial $I_{K\text{-}ACh}$ (K_D=0.03 μM) [43]. Activation of $I_{K\text{-}ACh}$ contributes to the net outward current augmentation that produces the epicardial AP notch and J wave formation. Furthermore, ACh increases parasympathetic tone by exerting cholinergic actions, which include negative chronotropism, which leads to a bradycardia-dependent J wave appearance [44]. ACh-induced muscarinic receptor activation inhibits inward I_{Ca} [45]. These direct actions of ACh shift the net transmembrane ionic current balance toward the outward direction. Koncz et al. established the aerobic ERS model of coronary-perfused canine heart preparation using pilsicainide (I_{Na} blocker), pinacidil ($I_{K\text{-}ATP}$ opener), verapamil (I_{Ca} blocker), and ACh as a cholinergic agent [27]. BrS shares some characteristic features of inherited channelopathy with ERS. Yan and Antzelevitch [46] actually demonstrated ACh-induced epicardial AP dome depression and ST elevation in an arterially perfused myocardial wedge preparation as an experimental model of BrS (Fig. 4). Noda et al. reported that, clinically, right, but not left, coronary ACh infusion

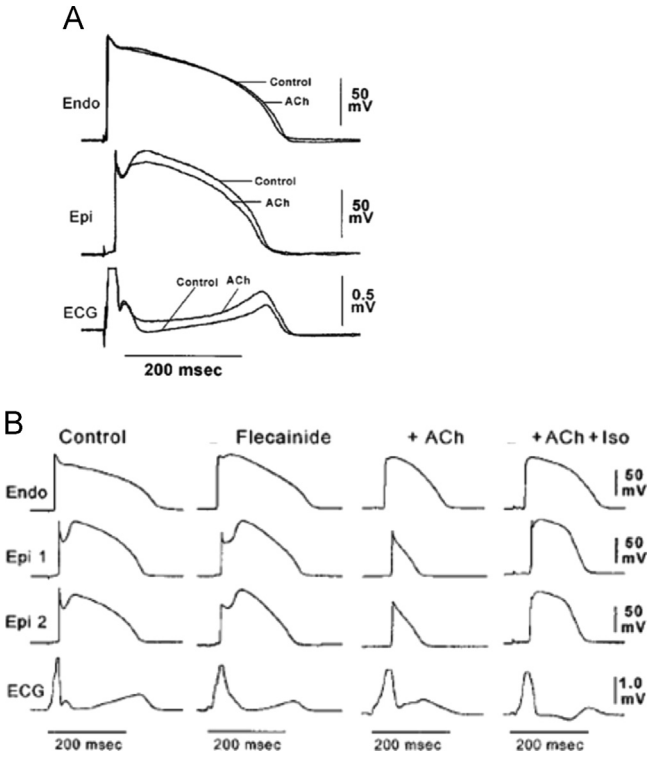

Fig. 4. In arterially perfused canine myocardial wedge preparations (A), acetylcholine (ACh) (3 μm/L) reduces dome amplitude in the epicardial action potential (AP) and elevates the ST segment in a transmural electrocardiogram (ECG). In another preparation (B), flecainide (7 μm/L), a potent Na channel blocker, is applied. Thereafter, ACh (2 μm/L) causes loss of the AP dome in the epicardium, but not in the endocardium, and ST segment elevation in a transmural ECG under the presence of flecainide. Isoproterenol (0.5 μm/L) restores these epicardial AP configurations and ECG changes [46].

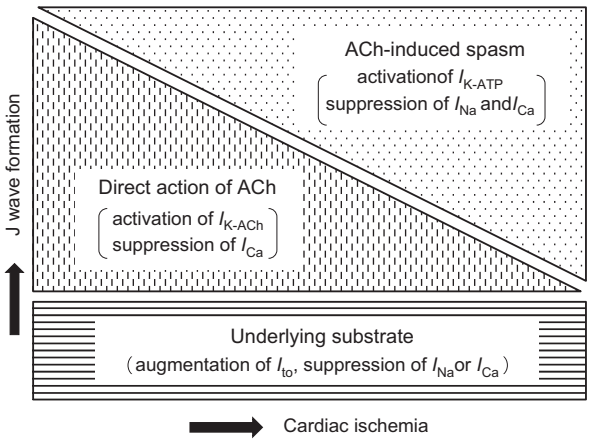

Fig. 5. A schematic illustration of the mechanisms of J wave formation from the viewpoint of epicardial transmembrane ionic currents as it relates to cardiac ischemia.

tends to elevate ST segment in the right precordial leads, without coronary spasm in patients with BrS [47]. These experimental and clinical studies indicate that ACh unmasks ERS, which is not mediated by ACh-induced coronary spasm.

3. Conclusions

In addition to coronary vasomotor regulation, the pathophysiological mechanisms of J wave manifestation on surface ECGs were reviewed by focusing on the electrophysiology and basic pharmacology of ACh, which may have a role as a potential diagnostic probe of J wave syndromes. ACh unmasks the J waves; this is mediated by $I_{K\text{-}ATP}$ activation in ischemic conditions and by direct cholinergic effects of ACh on $I_{K\text{-}ACh}$ activation in non-ischemic conditions. These ligand-gated K^+ channel activations increase background K^+ conductance and shift the balance of epicardial transmembrane ionic currents toward the outward direction. There may be intermediate conditions between the distinct ischemic and non-ischemic states, where heterogeneous epicardial augmentation of I_{to}, in addition to reduced I_{Ca} and I_{Na}, might be the persistent underlying substrate of the J wave syndrome (Fig. 5). Basic studies using canine ventricular tissue and cell preparations confirmed this possibility [25], which is also suspected by a case presenting de novo appearance of J waves without evidence of coronary spasm under the cumulative intracoronary application of ACh [39]. However, a prospective cohort of ACh application tests, widely conducted in catheterization laboratories, is required to strengthen the conceptual framework (Fig. 5) regarding the hypothetical ACh challenge test of ERS.

Disclosures

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Conflict of interest

All authors declare no conflict of interest related to this study.

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