REVIEW ARTICLE

Indication for electrophysiological study in practice

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SUMMARY

During the past 35 years cardiac electrophysiological studies have evolved into widely employed standard clinical tools in the diagnostics of the different symptoms - unexplained syncope or palpitations etc.- and in the management of different cardiac arrhythmias. This review article presents current opinion regarding the indications and interpretations of invasive electrophysiological studies in the bradyarrhythmias and in supraventricular and ventricular tachyarrhythmias. It is stressed that in the course of these studies, therapeutic catheter ablation procedures are being performed nowadays in many cases. Finally, the role of programmed ventricular stimulation in risk stratification of patients with ischemic and non-ischemic cardiomyopathy is discussed. It is emphasized that non-pharmacological treatment of clinically significant brady- and tachyarrhythmias is the dominant therapeutic option at present. The dynamical progress in this field of cardiology may require periodic updating of the indications for electrophysiological studies as well as the evaluation of their contribution to the treatment of arrhythmias and to the assessment of serious arrhythmia risk on which prophylactic therapy may be based.
Key words: arrhythmia, clinical electrophysiology, programmed ventricular stimulation, sudden cardiac death.

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Invasive electrophysiological study (EPS) is a diagnostic method suitable for specification of the type of arrhythmia, its mechanism and prognostic significance, and it contributes to the rational selection of therapy, management and evaluation of therapeutical effect. In most tachycardias, EPS may be directly followed by catheter ablation (1, 2).

The evaluation of the present development of EPS provides evidence that the era of electrophysiology has been started by using of programmed electrical heart stimulation that served the study of the mechanisms of tachycardia origin and by recording of His bundle electrogram by means of electrode catheter, introduced intracardially by intravenous access (3, 4). In the beginning, this examination was used mainly in bradyarrhythmias for specification of localization and prognostic significance of disturbances of atrioventricular conduction and sinus node dysfunction (5-7). Clinical use of EPS gradually orientated much more to tachyarrhythmic disorders. It served for the specification of supraventricular (SVT) and ventricular tachycardias (VT), for evaluation of inducibility of arrhythmias and for evaluation of the influence of antiarrhythmics on inducibility of arrhythmias (8-11). EPS was also used for preoperational diagnostics, indication and evaluation of the effect of surgical treatment of tachycardias (12–14). The experience from the surgical therapy of tachycardias was subsequently utilized and extended during the development of catheter ablation technique, which was first focused on the regular supraventricular and subsequently on ventricular tachycardias and, recently, on atrial fibrillation (15–18). Recently, EPS has been also used within risk stratification of sudden cardiac death and indication of cardioverter-defibrillator (ICD) implantation (19–21).

Tab. 1. Classification of indications for electrophysiological study into 3 classes– by criteria of the evidence-based medicine (2, 22, 23,40)

Class I:	Unequivocal indications (All experts agree that EPS is useful and important for patient treatment and patients with these condition benefit from EPS)
Class II:	Possible, but still equivocal indications (There is less certainty about usefulness of the information from EPS for further therapeutical procedure)
	a- proofs and standpoints largely *support that*
	b- proofs and standpoints are *less clear* for the present
Class III:	Unsuitable indications (EPS does not provide useful information)
Level of evidence: A - C	
A.	The data were derived from multiple randomized clinical trials or meta-analyses
B.	The data are based on one randomized trial, or on large non-randomized studies
C.	The primary basis for the recommendation was expert consensus, small non-randomized or retrospective studies or observational registries

Recommendations for indication or performance of EPS, widely accepted, are included in many reports dealing with tachyarrhythmia therapy, sudden death prevention and use of implantable devices (2, 22–24). The indications are divided into three classes in accordance with evidence-based medicine (Tab. 1). The conditions necessary for the safe performance of EPS and the

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criteria for obtaining of competence for performing these invasive examinations are stated (25). The recommendations of the Czech Society of Cardiology (Česká kardiologická společnost) dealing with the above-mentioned topics are summarized in the contemporary version of guidelines. The indication criteria, mentioned in these recommendations, correspond with Class I indication and in some cases with Class II-a of the cited foreign reports.

INDICATION FOR EPS IN BRADYARRHYTHMIAS

Permanent cardiac pacing is a highly effective therapeutical procedure in clinically significant bradyarrhythmias. In most patients with bradyarrhythmia various forms of ECG recording may be fully sufficient for the establishment of precise diagnosis and a decision about treatment options (22, 24, 27, 28). EPS is indicated if the symptoms suspicious of being caused by bradyarrhythmia are not explicable by ECG recording or if it is not attainable. EPS may contribute to the diagnosis of sinus node dysfunction. Prolongation of sinus node recovery time (SNRT) over 550 ms has about 50% sensitivity and specificity for detection of clinically significant sinus node dysfunction (22). For EPS mildly symptomatic patients are indicated with 2nd degree atrioventricular blockade or with bifascicular blockade in whom markedly prolonged HV interval (over 90–100 ms) detected on His bundle electrogram or infra-His conduction block (spontaneous or during atrial stimulation) reveals prognostically serious conduction disorder, localized in distal parts of His-Purkinje system. This finding is an indication for permanent cardiac pacing (24, 27, 28) (Fig 1).

Tab.2. Benefit of electrophysiological study in supraventricular tachycardias (SVT)

Specification of SVT type:
- Manner of induction of SVT
- Atrial activation sequence during SVT
- Linkage of atrial and ventricular activity during origin and maintenance of SVT
- Effect of atrial and ventricular stimulation on SVT
- Effect of drugs and vagal manoeuvers on SVT

Catheter ablation directly follows

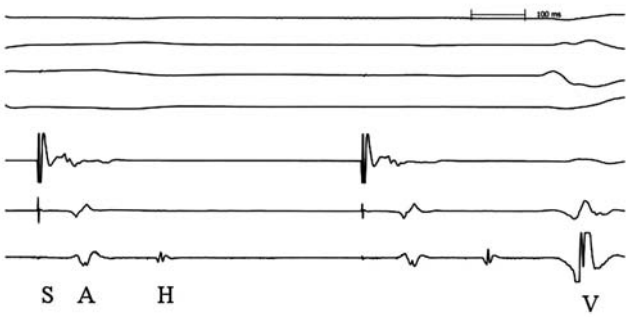

Fig.1. His-bundle electrogram with pattern of infra-His blockade appearing during atrial stimulation
In conducted atrial activity to the ventricle (the right part of the Figure) there is apparent prolongation of HV interval reflecting the conduction through His-Purkinje system. It is apparent in the left part of the Figure that the atrial activity following the stimulus is not conducted to the ventricle, and blockade distal to His deflection is apparent (i. e. infra-His location).
S - stimulus, A - atrial activity, H - His-bundle activity, V - ventricular activity

INDICATION FOR EPS IN TACHYARRHYTHMIAS

EPS is a "gold standard" for more precise diagnostics and differential diagnosis of tachycardias. It should be emphasized that 12-lead ECG remains the base of diagnostics in clinical tachycardia.
Reminder 1: If the patient's condition allows, it is necessary to perform *12-lead ECG* during clinical symptoms of (spontaneous) tachyarrhythmia!

EPS IN SUPRAVENTRICULAR TACHYARRHYTHMIAS (SVTA)

SVTA is a heterogeneous group of heart rhythm disorders, for whose origin and maintenance, the tissue above the ramification of His bundle (atrial musculature, atrioventricular or sinoatrial node) is

Tab.3. Indication of electrophysiological study in supraventricular tachyarrhythmias (by the guidelines of the European Society of Cardiology (2))

Class I indication:
- Differential diagnosis of tachycardias with broad QRS
- Regular SVT with indication to catheter ablation (first choice treatment in most SVT)
- Atrial fibrillation in ventricular preexcitation (WPW type)

Class II-a indication:
- Asymptomatic patients with ventricular preexcitation (WPW type)

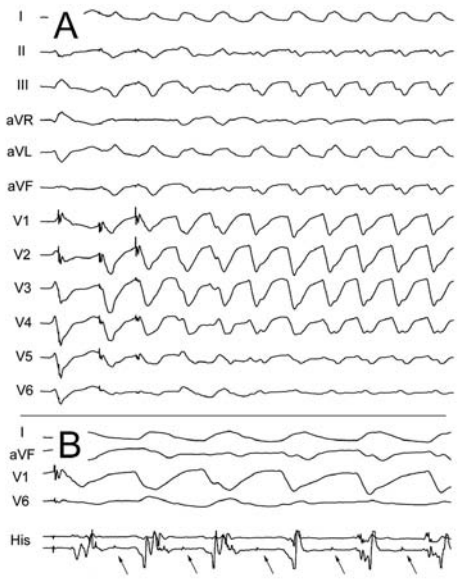

Fig. 2. Induction of ventricular tachycardia, type bundle branch reentry tachycardia (BBRT), by programmed ventricular stimulation
In the upper part (A) of this Figure, there is 12-lead ECG record, in the lower part (B) there is simultaneous record of His-bundle electrogram. The arrows mark His-bundle potentials that precede ventricular activity, long HV interval is apparent.

essential. The analysis of the large population of the patients shows the representation of individual types of SVT: atrioventricular nodal reentry tachycardia (AVNRT) is represented by more than 50%, more than 1/3 is constituted by AV reentry tachycardia (AVRT), caused by the presence of manifest or latent (only retrograde conduction) accessory atrioventricular connection. The remaining about 10% of cases are paroxysmal or persistent atrial (reentry or automatic) or sinoatrial nodal reentry tachycardia or inappropriate sinus tachycardia (1). In this SVTA classification, atrial flutter and atrial fibrillation are classified as the detached entities. Contribution and indication of EPS in SVTA are summarized in the Tables 2 and 3. It can be concluded that EPS (followed by catheter ablation) is indicated in all symptomatic types of SVT.

Catheter ablation is the first choice therapeutical approach in these cases.

Reminder 2: In the majority of SVT, diagnostic part of *EPS is directly followed by therapeutical catheter ablation!* The patient must be informed before the procedure about this possibility of treatment.

In asymptomatic patients with ECG pattern of ventricular preexcitation, EPS may detect the more risky type of this abnormality. A large prospective study demonstrated that short antegrade effective refractoriness of AV conduction and inducibility of SVT imply manifold increased risk of occurrence of clinical SVTA during the following 3-year period (29).

INDICATION OF EPS IN VENTRICULAR TACHYARRHYTHMIAS (VTA) AND IN RISK STRATIFICATION OF SUDDEN CARDIAC DEATH

VTAs occur in various forms and have various hemodynamic and prognostic seriousness. Despite of SVTA, in which therapy is often based on the patient's symptoms, the prognostic criteria of VTA, i. e. assessment of risk of hemodynamically serious VTA and sudden cardiac death (SCD), are pivotal for the indication and choice of therapy. This risk is first of all due to the presence and seriousness of the structural cardiac disease. The risk stratification by means of EPS evaluates the sustained ventricular tachycardia inducibility during the administration of programmed electrical stimuli.

Many studies dealt with methodology of this testing and evaluation of influence of number of "extrastimuli", their energy, coupling intervals, site of stimulation and premedication before the examination (1, 30). The following recommendation for performing programmed ventricular stimulation is the conclusion of the studies:

Sequentially, 1–3 premature stimuli are applied in the presence of sinus rhythm and in 2 basic stimulation frequencies (with length of cycle 600 ms and 400 ms) from the apical part and outflow tract of the right ventricle. Coupling interval of the premature stimuli should be longer than 200 ms, because stimulation with shorter coupling intervals might lead to non-specific response (1, 22, 26, 30).

Reminder 3: During the standard programmed ventricular stimulation, at most 3 premature stimuli should be delivered and their coupling interval should not be shorter than 200 ms. Too much aggressive stimulation protocol may lead to non-specific response with no predictive significance.

Tab.4. Relation of the left ventricle ejection fraction and inducibility of s-VT to the mortality in the patients with coronary artery disease (MUSTT results in 1,791 patients with EFLV≤0.4 and spontaneous ns-VT) (33)

		5-year mortality	
	N	Total	SCD
EFLV<0.3, EPS+	(217)	57%	40%
EFLV<0.3, EPS-	(690)	54%	31%
EFLV≥0.3, EPS+	(212)	43%	30%
EFLV≥0.3, EPS-	(672)	34 %	17%

EPS+ – s-VT induced on electrophysiological study, EPS- – s-VT not induced on electrophysiological study, N – number of patients, SCD – mortality due to sudden cardiac death

EPS in complex forms of ventricular extrasystoles(VES) has no indication in class I (22, 26). EPS is recommended in class II indication in symptomatic, very frequent monomorphic ventricular extrasystoly, not responding on pharmacological therapy or if a patient does not tolerate the pharmacotherapy or if he/she prefers catheter ablation procedure (22, 23). Of course, the evaluation of suitable indication is individual and takes into account other clinical indicators, the expected effect and risk of non-pharmacological therapy.

EPS in non-sustained VT (ns-VT) is useful for the risk stratification of SCD especially in the patients after myocardial infarction with some degree of left ventricle systolic dysfunction (18, 21, 26–29). Inducibility of s-VT has sensitivity about 60–65%, specificity about 85% and negative prognostic value up to 95% for the risk assessment of clinical s-VT or SCD. The problem is – as in other risk stratification tests – the low positive predictive value (about 25%) (26, 27). Limitation of the result of EPS is the fact that the finding is valid only in stabilized clinical condition and only for shorter period of follow-up.

In "thrombolytic era" of myocardial infarction (MI) therapy, the risk of severe postinfarction left ventricular dysfunction is lowered thanks to the early recanalization of infarcted vessel. Despite the early coronary interventions in acute coronary syndrome, the increased risk of SCD after MI persists in the portion of patients. So far, so-called two-stage risk stratification has been recommended, when first non-invasive procedures – echocardiography (for the assessment of the left ventricle size and systolic function) and Holter ECG monitoring - are indicated for detection of ventricular arrhythmias (19–21, 23). If decreased left ventricle systolic function with ejection fraction (EF)<40% is detected, EPS is indicated. If during electrophysiological examination s-VT is induced and this inducibility lasts even after administration of antiarrhythmic drug (by the recommendation of the Czech Society of Cardiology – class III antiarrhythmic drugs), then implantation of ICD is indicated as so called primary prevention (27, 31, 32). The results of MUSTT study provided evidence that in lowered LVEF in the range of 30–40%, inducibility of s-VT during EPS predicts significantly higher risk of SCD (Tab. 4) (33). In the patients with markedly lowered LV function, with EF <30% with broadened QRS complex over 120 ms, primary prophylactic implantation of ICD is preferred, without further risky stratificiation (34, 25). On the basis of recommendation of the European Society of Cardiology, this indication is for the present incorporated into II-a class (32). Nevertheless, the question does not have a clear answer. The next analyses of MADIT II study showed that ICD application benefit the patients who were enrolled into the study after longer interval (more than 18 months) after MI (36). So it is obvious that the risk of s-VT after MI is time-dependent and is probably determined by electrophysiological and structural remodelling after MI (36, 37). It is very probable that the predictive value of EPS findings will be different in the same patient, if the examination is performed in different stages of healing and myocardial remodelling after MI. More precise answers can be expected from further experimental and clinical studies. The attention should be paid to the evaluation of attained myocardial revascularization and entire coronary arterial circulation and to the development of effective antiremodelling therapy (37, 38). In chronic heart failure

and in non-ischemic cardiomyopathies, EPS is of lesser significance in prediction of risk of SCD than in LV dysfunction after MI (33). In dilatation of heart ventricle, EPS may demonstrate tachycardia on the basis of macroreentry in bundle branch system – so-called bundle branch reentry tachycardia, which has its characteristic signs and can be easily removed by catheter ablation of the right bundle branch (1) (Fig. 2).

Reminder 4: The *validity of EPS* in structural heart disease is short-lasting. So-called *electrical stability* of myocardium *changes dynamically* together with changes of health condition, with development of *myocardial remodelling* and in consequence of other factors.

The significance of EPS in sustained or frequent monomorphic VT (MVT) is similar to that in SVT: it serves for detection of arrhythmogenic mechanism, and by means of endocardial mapping it serves for the location of arrhythmogenic substrate, and the region of myocardial tissue inside the substrate which is critical for creation and sustaining of MVT. In the involved location, radiofrequency or other energy is delivered to achieve catheter ablation of the arrhythmogenic area. In idiopathic VT, the effectivity of catheter ablation is about 85–90%, in MVT with structural heart disease the effectivity of this treatment is 60–70% depending on severity of the underlying heart disease, extent of the damaged tissue and experience of the specialist performing the catheter ablation. Risk of clinically significant complication is about 4% in this complex procedures (39).

Reminder 5: The patient should be preferably referred to the hospital facility that is able to treat the patient adequately to the primary cardiac involvement and to provide the complex therapy of arrhythmia (including catheter ablation and ICD implantation).

EPS IN SYNCOPAL EVENTS

In the patient with a syncope of unclear origin, EPS is also the possible part of the diagnostic algorithm that can elucidate arrhythmic origin of the syncopal events (23, 24, 40). On the basis of the new guidelines of the European Society of Cardiology, class I indication for EPS include the conditions in which the initial examination signals the possibility of arrhythmic cause of the syncope.

The next indication (in class II) is ruling out cardiac cause of syncope in the patients with a "risky profession" (40). The result of EPS is supposed to be diagnostic for elucidation of arrhythmic cause of syncope if the following findings are present (23, 40):

- sinus bradycardia with significantly prolonged SNRTc,
- bifascicular blockade with HV≥100 ms or with IInd or IIIrd degree blockade, localized intra-His or infra-His (during incremental atrial stimulation) or thus localized blockade of higher degree, unmasked by intravenous ajmalin, disopyramide or procainamide administration,
- inducibility of sustained monomorphic VT,
- inducibility or rapid SVTA leading to the manifestation of symptoms due to hypotension or corresponding spontaneously occurring symptoms.

Similarly, as in examination of unclear syncopal events, the role of EPS is evaluated in severe cases of sporadically occurring *palpitations,* in which ECG record was not obtained during the episodes. EPS in these events may detect various types of paroxysmal SVT and VT, therapy of which then should meet the usual standard procedures.

CONCLUSION

Taken together, EPS remains the irreplaceable examination in many aspects, which is used for specification of tachycardia type, for indication, management and follow-up of non-pharmacological treatment. The significance of EPS for the risk stratification is emphasized in connection with the next indicators (as lowered LVEF) especially in the patients after MI. In other cardiac disorders, the significance of EPS is much lesser.

EPS should be performed only in the facilities that are able to provide the appropriate complex therapy of the underlying cardiac disease and the detected arrhythmia. If catheter ablation therapy of the diagnosed arrhythmia is indicated, it is usually directly followed by EPS.

Perspectively, growing knowledge about patophysiological base of tachyarrhythmias will make possible to use for the evaluation of the effect of therapy and for the assessment of the patient@s prognosis other - up to now less explored - indicators of EPS. These, in connection with other tests, will provide new information about the stage and development of negative electrophysiological remodelling and its possible positive influencing by various therapeutical procedures or their combinations.

Abbreviations

AV	- atrioventricular
AVNRT	- atrioventricular nodal reentry tachycardia
AVRT	- atrioventricular reentry tachycardia
ECG	- electrocardiogram
EPS	- electrophysiological study
HV	- interval on His-bundle electrogram
ICD	- implantable cardioverter-defibrillator
LV	- left ventricle
LVEF	- ejection fraction of the left ventricle
MADIT II	- Multicenter Automatic Defibrillator Implantation Trial –II
MI	- myocardial infarction
MUSTT	- Multicenter Unsustained Tachycardia Trial
MVT	- monomorphic ventricular tachycardia
ns-VT	- non-sustained ventricular tachycardia
QRS	- ventricular complex on ECG
SCD	- sudden cardiac death
SNRTc	- corrected sinus node recovery time
SVT	- supraventricular tachycardia
s-VT	- sustained ventricular tachycardia
SVTA	- supraventricular tachyarrhythmia
VES	- ventricular extrasystoles
VT	- ventricular tachycardia
VTA	- ventricular tachyarrhythmia

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