Heterogeneity of Activation Recovery Interval and Restitution in Non-Ischemic Cardiomyopathy and its relation to Ventricular Arrhythmias

Published: 02-03-2015
Last updated: 21-04-2024

Primary Objectives: 1. To assess the values of ARI and APDR in NICM patients. 2. To assess the three-dimensional heterogeneity of ARI and APDR in NICM patients.3. To compare 1. and 2. with the same data collected from non-NICM patients.4. To...

Ethical review	Approved WMO
Status	Pending
Health condition type	Cardiac arrhythmias
Study type	Observational invasive

Summary

ID

NL-OMON41046

Source
ToetsingOnline

Brief title
ARI/Restitution

Condition

- Cardiac arrhythmias

Synonym
Life-threatening arrhythmias, Ventricular Arrhythmias

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Activation Recovery Interval (ARI), Non-Ischemic Cardiomyopathy (NICM), Repolarization, Restitution

Outcome measures

Primary outcome

Electroanatomical mapping data: ARI and APDR values (derived from unipolar

signals) from predefined sites

Inducibility and type of VA during electrophysiology study

Inducibility and type of VA during ARI/APDR pacing protocol

Occurrence and type of spontaneous VA during 24 month follow-up

Secondary outcome

Mortality (all cause, cardiac, arrhythmic)

Study description

Background summary

Ventricular arrhythmias (VA) are a common cause of sudden cardiac death[1]. However, different substrates and mechanisms may operate in the heterogeneous group of non-ischemic cardiomyopathy (NICM) patients with VA. Previously focus has been placed on the role of depolarization abnormalities and anisotropic conduction resulting in conduction delay and unidirectional conduction block. These are the preconditions for fixed re-entry often observed in patients with ventricular scar and monomorphic ventricular tachycardia. However, in patients with NICM, polymorphic, pleomorphic VT and ventricular fibrillation is often observed, likely due to a different mechanism. There is little data on the potential role of heterogeneity in repolarization, which may play an important role in the arrhythmogenesis in NICM VA.

Activation Recovery Intervals (ARI) are considered reliable surrogates for Action Potential Duration (APD) and as such provide insight into repolarization duration.[2] [3] Small studies have shown that apico-basal heterogeneity in ARI

exists in patients at higher risk for VA [4] and this heterogeneity may play a role in sympathetic induced arrhythmias as demonstrated in an animal model [5]. However, the majority of the few included patients had prior myocardial infarction with compact scars, suggesting that induced VTs are likely due to slow conduction and scar related re-entry. In addition, for evaluation of epicardial ARIs the venous system has been used, restricting measurements to limited epicardial sites such that an evaluation of endocardial/epicardial 3-dimesional heterogeneity could not be performed. Finally, normal values obtained in patients without structural heart disease are sparse. We propose that a certain amount of apico-basal heterogeneity is to be expected but that 3 dimensional analysis of the variation in ARI is necessary to determine its role in the arrhythmogenesis of NICM VA.

Action Potential Duration Restitution (APDR) relates an APD to its proceeding diastolic interval (DI). Research has suggested that steep APDR curves promote wave breaks and fibrillation [6, 7]. Cut-off valves of Restitution curves necessary for VF have been proposed, [8] and these values are supported by current clinical research[9, 10], but these values have never been validated in humans with NICM. We hypothesise that it is not the value of APDR but rather the heterogeneity of this parameter that indicates arrhythmogenicity.

Understanding of ARI and APDR heterogeneity in NICM patients will provide insights into the substrate and potential mechanisms of VA. Knowledge of the mechanism is mandatory for treatment and risk stratification. The proposed method of data acquisition using standard catheter techniques may have important clinical and practical implications.

References:
1. Bayes de Luna, A., P. Coumel, and J.F. Leclercq, Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J, 1989. 117(1): p. 151-9.
2. Coronel, R., et al., Monophasic action potentials and activation recovery intervals as measures of ventricular action potential duration: experimental evidence to resolve some controversies. Heart Rhythm, 2006. 3(9): p. 1043-50.
3. Haws, C.W. and R.L. Lux, Correlation between in vivo transmembrane action potential durations and activation-recovery intervals from electrograms. Effects of interventions that alter repolarization time. Circulation, 1990. 81(1): p. 281-8.
4. Chauhan, V.S., et al., Increased ventricular repolarization heterogeneity in patients with ventricular arrhythmia vulnerability and cardiomyopathy: a human in vivo study. Am J Physiol Heart Circ Physiol, 2006. 290(1): p. H79-86.
5. Ajijola, O.A., et al., Functional differences between junctional and extrajunctional adrenergic receptor activation in mammalian ventricle. Am J Physiol Heart Circ Physiol, 2013. 304(4): p. H579-88.
6. Taggart, P., et al., Effect of adrenergic stimulation on action potential duration restitution in humans. Circulation, 2003. 107(2): p. 285-9.
7. Ng, G.A., et al., Sympathetic nerve stimulation produces spatial

heterogeneities of action potential restitution. Heart Rhythm, 2009. 6(5): p. 696-706.
8. Weiss, J.N., et al., Chaos and the transition to ventricular fibrillation: a new approach to antiarrhythmic drug evaluation. Circulation, 1999. 99(21): p. 2819-26.
9. Garfinkel, A., et al., Preventing ventricular fibrillation by flattening cardiac restitution. Proc Natl Acad Sci U S A, 2000. 97(11): p. 6061-6.
10. Hayashi, M., et al., Ventricular repolarization restitution properties in patients exhibiting type 1 Brugada electrocardiogram with and without inducible ventricular fibrillation. J Am Coll Cardiol, 2008. 51(12): p. 1162-8.

Study objective

Primary Objectives:
1. To assess the values of ARI and APDR in NICM patients.
2. To assess the three-dimensional heterogeneity of ARI and APDR in NICM patients.
3. To compare 1. and 2. with the same data collected from non-NICM patients.
4. To correlate inducibility, type and occurrence of spontaneous VA with findings in 1. and 2.

Secondary Objective:
1. To compare findings from Primary Objectives 1. and 2. with ECG parameter (depolarisation, repolarisation), electrophysiology parameters obtained during routine Electrophysiology study (Ventricular Refractory Period) and mapping (total activation time, local conduction delay, unipolar voltage)

Study design

This will be a single-center prospective observational case-control study.

Study burden and risks

Risk
In all patients, the electrophysiological study and mapping procedure will be clinically indicated and scheduled before inclusion in the study. The technique will be performed according to current standards. The only change introduced by this protocol will be a slightly longer procedure time. During procedures *down time* regularly exists: time in which mapping data is reviewed, before ablation is performed. As much as possible the data collection for this protocol will be conducted in this *down time* and as such will not add additional procedural time. If it is not possible to collect data during *down time* the procedure will be lengthened by a maximum of 35 minutes.
Benefit
Patients in the case group may not directly benefit from participating in this study. However, insights in potential VA mechanism not approachable by catheter

techniques may help to select other treatment strategies like antiarrhythmic drugs. This study is likely to provide new insights that improve therapy for VA which may be applied to study participants in the future.
Patients in the control group may benefit from participating in this study if previously unrecognized arrhythmic pathologies are discovered during the procedure.

Future patients
Future patients with NICM will probably benefit most from this study. This study may
improve our understanding of the substrate and mechanism of VA in NICM patients, so that more effective, individualized and substrate-based treatments of VA can be applied and further developed. Such a treatment may significantly reduce morbidity and mortality of VA in NICM patients. Furthermore, this study may improve risk stratification for VA in NICM. This may allow more efficient allocation of preventative therapies (e.g. ICD implantation). Although NICM patients are the group of interest in this proposal/research protocol, the proposal may be applicable to larger groups of patients suffering from various diseases leading to cardiac arrhythmias.

Contacts

Public
Leids Universitair Medisch Centrum

Postbus 9600 Albinusdreef 2
Leiden 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Postbus 9600 Albinusdreef 2
Leiden 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Cases: This population will consist of consecutive NICM patients with previous documentation of ventricular arrhythmias (sustained monomorphic VT, polymorphic VT or ventricular fibrillation) scheduled for epicardial or endocardial electrophysiological study with or without ventricular tachycardia ablation.
Controls: This group will consist of consecutive patients without structural heart disease referred for mapping and ablation of idiopathic Premature Ventricular Contractions.

Exclusion criteria

All subjects:
Age < 18 years
Inadequate patient competence
Pregnancy
Inability to comply with the protocol due to haemodynamic instability
Non-NICM
Control specific:
Previous history of ventricular arrhythmias
Known pro-arrhythmic genetic mutation or disease

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2014
Enrollment:	45
Type:	Anticipated

Ethics review

Approved WMO

Date:	02-03-2015
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL50746.058.14