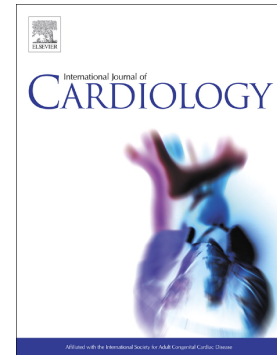


Is it possible to predict and prevent sudden cardiac death as a first manifestation of cardiac disease?

Heikki V. Huikuri, M. Juhani Junttila



PII: S0167-5273(19)35040-5

DOI: <https://doi.org/10.1016/j.ijcard.2019.11.113>

Reference: IJCA 28146

To appear in: *International Journal of Cardiology*

Received date: 12 November 2019

Accepted date: 15 November 2019

Please cite this article as: H.V. Huikuri and M.J. Junttila, Is it possible to predict and prevent sudden cardiac death as a first manifestation of cardiac disease?, *International Journal of Cardiology*(2018), <https://doi.org/10.1016/j.ijcard.2019.11.113>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Is it possible to predict and prevent sudden cardiac death as a first manifestation of cardiac disease?

Heikki V Huikuri, MD, M Juhani Junttila, MD

Research Unit of Internal Medicine, Medical Research Center, University of Oulu and University Hospital of Oulu, Finland

Correspondence: Prof. Heikki Huikuri, Research Unit of Internal Medicine, Medical Research Center, University of Oulu and University Hospital of Oulu, Finland, e-mail: heikki.huikuri@oulu.fi

In this journal, de Ferrari et al. report the results of PREDESTINATION study, which is an Italian case-control, prospective multicenter study assessing the risk factors of ventricular fibrillation (VF) occurring during the early hours after onset of symptoms of their first myocardial infarction.¹ The investigators must be congratulated for the excellent multicenter study design. It has been proposed that VF during the acute ischemic event is perhaps the most common mechanism of sudden cardiac death, especially in those without a previously diagnosed cardiac disease.² Fatal arrhythmia often occurs early after the onset of symptoms before the patient reaches the hospital or emergency care. Furthermore, in about one half of these patients sudden cardiac death is the first clinical manifestation of their cardiac disease. There is relatively little information about the factors that predispose to fatal arrhythmia at the time of first acute coronary event. Despite the nice study protocol, the study design does not provide much additional clinically relevant information to the global problem of sudden cardiac death. In this study, the risk profile before the ischemic event was not well known and some of the observed risk factors are not modifiable. Large epidemiological follow-up or case-control studies are needed to answer these questions. In addition, VF as an initial rhythm of out of hospital cardiac arrest is declining while asystole and pulseless electrical activity have become more common.³

Investigators were able to find five factors that predicted VF during MI; such as hypokalemia, anterior infarction, low systolic blood pressure, physical inactivity, and family history of sudden cardiac death.¹ Many of these factors have been previously observed to be associated with VF. Hypokalemia has long been known to aggravate ventricular arrhythmias in various clinical settings. Low systolic blood pressure and anterior site of myocardial infarction are signs of larger infarction areas and more severe hemodynamic compromise, which may predispose to VF. The investigators speculate that quantitative dominant left-sided sympathetic nerves following anterior ischemia may lead to more common occurrence of VF in anterior vs. other infarction sites. This may be one contributing factor. Another explanation is that anterior infarctions are usually caused

by occlusion of left anterior descending coronary artery, which supplies a large myocardial territory. This causes a larger heterogeneity of impulse conduction and repolarization, which both can facilitate fatal ventricular arrhythmias by re-entry mechanism.

The association of physical inactivity and family history of sudden cardiac death deserve more comments. There is an evident relationship between physical activity and cardiac autonomic regulation. Inactive subjects have an impaired cardiac vagal regulation. The authors of this study have shown in the animal studies that low cardiac vagal activity is associated with VF at the time of coronary occlusion.⁴ Impaired autonomic regulation is a plausible explanation why subjects who have been physically inactive experience commonly VF at the time of an acute ischemic event.

Family history of sudden cardiac death has been previously shown to be risk marker of sudden cardiac death.^{5,6} These observations were confirmed in this study. AGNES study observed an association between a genetic variant and VF during MI.⁷ Subsequent larger genome-wide association meta-analysis between the victims of sudden cardiac death vs. controls have not confirmed this observation.⁸ The problem of these studies is the heterogeneity of populations, since the mechanisms of sudden cardiac death are variable. In this respect, the design of PREDESTINATION and other similar study designs study may provide more relevant information about the possible role of genetics in ischemic VF causing sudden cardiac death.

Few factors observed here associated with ischemic VF are modifiable and thereby have some clinical interest. Clinicians should pay attention and treat hypokalemia at the time of MI. Even mild-to-moderate physical activity seems to prevent ischemic VF. Thus, people should be encouraged to exercise, even if they do not reach the recommended levels. One cannot choose his or her family. However, as PREDISTINATION study is ongoing, it can be expected that modern genetic approaches by whole-genome sequencing techniques may reveal some gene variants, which can be used in risk stratification. Preventive therapeutic approaches could then be forwarded to high-risk subjects in order to prevent their first MI and encourage them to exercise more.

References:

1. De Ferrari GM, Dusi V, Ruffinazzi M, Masiello LC, Ruffino E, Cacciavillani L et al.
Risk factors for primary ventricular fibrillation during a first myocardial infarction. Clinical Findings from PREDESTINATION (PRimary vEntricular fibrillation and suDden dEath during firST myocardIal iNfArcTION): Int J Cardiol, in press
2. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias.
New Engl J Med. 2001 Nov 15;345(20):1473-82
3. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK .
Changing incidence of out-of-hospital ventricular fibrillation, 1980–2000
JAMA, 2001 288: 3008-3013
4. P.J. Schwartz, E. Vanoli, M. Stramba-Badiale, G.M. De Ferrari, G.E. Billman, R.D et al..
Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction
Circulation, 1987, 78: 969-979
5. Dekker LR, Bezzina CR, Henriques JP, Tanck MW, Koch KT, Alings MW et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. Circulation. 2006;114:1140-1145.
6. Kaikkonen KS, Kortelainen ML, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. Circulation. 2006;114:1462-1467
7. Bezzina CR, Pazoki R, Bardai A, Marsman RF, de Jong JSSG, Blom MT et al. Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction Nat Genet. 2010 Aug; 42:688-691.

8. Ashar FN, Mitchell RN, Albert CM, Newton-Cheh C, Brody JA, Müller-Nurasyid M et al.

A comprehensive evaluation of the genetic architecture of sudden cardiac arrest.

Eur Heart J. 2018 Nov 21;39:3961-3969.

Highlights

- The design of PREDESTINATION study is elegant
- 5 factors were associated with an increased risk of ventricular fibrillation during the first myocardial infarction
- future genetic studies may reveal genetic variants that predispose to sudden cardiac death