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Special Article

Arrhythmogenic right ventricular cardiomyopathy: clinical registry and database, evaluation of therapies, pathology registry, DNA banking

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A multidisciplinary collaborative European study has been designed with the aim to investigate the clinical, pathological and genetic features of arrhythmogenic right ventricular cardiomyopathy (ARVC), which is a progressive, genetically determined disorder of the right ventricular myocardium and a major risk of sudden death particularly in the young.[1–3] The disease is reported familial up to 50% with autosomal dominant inheritance while an autosomal recessive form (Naxos disease) associated with cutaneous abnormalities also exists. Nine genetic loci and mutations in three genes have been discovered so far.[4–7] Treatment and prevention of ventricular tachyarrhythmias and sudden death include antiarrhythmic drug therapy, catheter ablation and the implantable cardioverter-defibrillator.[2,8–11] However, a systematic evaluation of treatment options is not yet available.

The need to set up an International Registry for ARVC has been perceived since years and many attempts have been accomplished after the publication of the diagnostic criteria.[12–14] The European venture was not costless and a financial support was searched for. The occasion was given by the 5th Framework Programme of the European Community in the field of research and technological development called "Quality of Life and Management of Living Resources", Action lines 1999/c 64/14 1.1.1.–7.2 "Evaluation of therapies through multinational large scale study/trials" 7.3 "Optimised use of databases, registries, reagents and sample banks".[15] A successful application was submitted by G. Thiene, on behalf of a multinational consortium. The project involves seven European countries:

Italy	Institute of Pathological Anatomy (G. Thiene), Department of Clinical and Experimental Medicine, Cardiology (A. Nava) and Department of Biology, Genetics (G.A. Danieli), University of Padua
Germany	Department of Cardiology and Angiology, University Hospital of Münster (T. Wichter)
France	Institute de Cardiologie, Group Hospitalier Pitiè-Salpetriere, Paris (G. Fontaine)
United Kingdom	The Heart Hospital, University College of London (W. J. McKenna)

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Poland	Department of Pathology, Children's Memorial Health Institute (E. Czarnowska), Department of Noninvasive Cardiology and Congenital Heart Defects, Institute of Cardiology (E.K. Wlodarska)
Cyprus	Department of Cardiology, Nicosia General Hospital (L. Antoniades)

Objectives

The project consists of four main missions (Fig. 1):

(1) Clinical registry (Consortium). Because of the rarity of the disease, a large scale database is mandatory to collect significant number of patient population affected by either familial or sporadic forms, in order to prospectively evaluate the accuracy of clinical diagnostic criteria, the long term outcome and the efficacy of therapies. The clinical registry database has been constructed on the WEB after final release of data forms and integrated communication network. The reader can now access on line the registry presentation at: anpat.unipd.it/ARVC/. A part from index cases with a definite diagnosis of ARVC, family members will also enter the clinical registry and will be labelled as affected, uncertain or non-affected based upon the currently available diagnostic criteria. Uniform standardised protocols have been developed for clinical investigation in order to ensure a uniform collection of comparable data, i.e. echocardiography, electrophysiological study, RV-angiography, endomyocardial biopsy, and magnetic resonance imaging protocols.

(2) Evaluation of therapies and therapy-related risk stratification (responsible partner T. Wichter). The main scope is to evaluate long-term efficacy of empiric vs electrophysiologically guided antiarrhythmic drug therapy and nonpharmacological, interventional treatment including catheter ablation and implantable cardioverter-defibrillators. The aim is to develop management algorithms and thereby improve clinical management, treatment related risk-stratification and long-term survival.

(3) Pathology registry and tissue bank (responsible partner G. Thiene). A cardiac pathology registry has been set up to collect either heart specimens or endomyocardial biopsies of patients entering the clinical registry. It will be the opportunity of gaining an insight into the etiopathogenesis of the disease, including molecular pathology investigations to search for cardiotropic viral genomes. The pending issue of fatty infiltration of the right ventricular free wall in normal vs ARVC hearts will be specifically addressed. Detailed pathology, immunohistochemistry and histochemistry protocols as well as molecular pathology protocol for the analysis of RNA and DNA viral genomes have been developed. Moreover, an electron microscopy protocol has been set up.

(4) DNA banking (responsible partner G.A. Danieli). The task is to collect DNA samples from blood of either sporadic or familial cases, to determine gene loci by linkage analysis and to identify specific abnormal genes by sequential analysis. This will allow mutation screening on

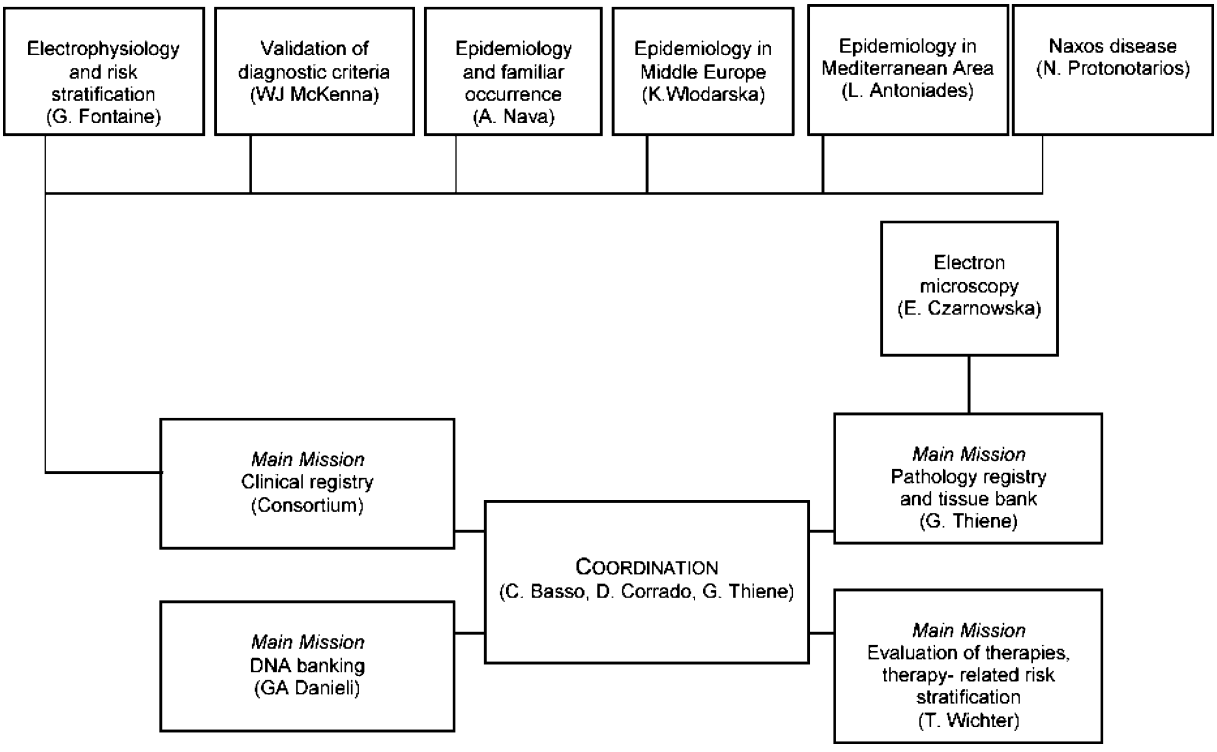

Fig. 1 Graphical representation of the project workplan: main missions and sub-missions, coordination.

families as well as genotype-phenotype correlations. To this aim, a protocol for blood sampling and/or DNA extraction as well as the informed consent form (if required from the national ethical committee) was developed.

All these protocols have been disseminated to the clinical services of the European Clinical Units and are available on the WEB.

Financial support and project management

The project, lasting 4 years (2001—2005) and funded by the European Community (QLG1-CT-2000-01091), is coordinated in by G. Thiene and two associated Coordinators (C. Basso and D. Corrado) in Padua, Italy and steered by a Steering Committee (Consortium). The Working Groups "Myocardial and Pericardial Diseases", "Ar-Arrhythmias" and "Developmental Anatomy and Pathology" of the European Society of Cardiology, as well the Scientific Council on Cardiomyopathies of the World Heart Federation are supporting the project and will represent the ways for exploitation and dissemination of the results of this multi-institutional investigation.[16]

Ethical aspects

A patient enrolled in the ARVC Registry is not exposed to any additional risk. Diagnostic testing, both invasive and non-invasive, is performed by the patient's physician during diagnostic work-up on clinical indications and will not be carried out solely for this program.

All the clinical sites did apply and obtained authorization from the local Ethical Committees for Registry participation. All reasonable measures have been taken to ensure privacy and confidentiality of participating subjects. Registry participants will be identified by a unique alpha-numerical code in the database. All blood samples and patient information stored in the computerized database are identifiable only by a code.

Preliminary achievements, exploitation and mid-term review

Two new gene mutations accounting for autosomal dominant ARVC have been discovered during the first two years of the project, i.e. ryanodine receptor 2 gene and desmoplakin mutation[4,5] as well as confirmation of locus assignment and mutation screening of four candidate genes in ARVD1.[6] The mutations in the gene encoding plakoglobin and ryanodine receptor 2 permitted genotype-phenotype correlation both in Naxos ARVC and ARVD2.[17–19] Finally, the need to broaden diagnostic criteria has been highlighted by prospective evaluation of relatives of ARVC patients[20] suggesting that only the advent of genetic testing will provide the gold standard for diagnosis. Furthermore, additional publications have been produced with the aim to exploit the ARVC clinical registry and tissue-DNA banks.[21–25]

A successful mid-term review meeting took place at the beginning of year 2003 with the participation of the project consortium and an independent expert reviewer.

International collaborations

A parallel research project has been funded in USA by the National Institute of Health (NIH) under the leadership of F.I. Marcus.[26] The NIH study is using similar data forms and computerized database which will facilitate further collaboration between the American and European researchers. G. Thiene and T. Wichter are serving the NIH project as Core Laboratories for Pathology and Angiography, respectively. Moreover, G.A. Danieli is collaborating for genetic investigations. In the frame of the European ARVC project, collaborations on basic research have been established with overseas centres.[6,27,28]

Call for other European cardiologist/scientists

Patient enrolment will be possible through data quality check by the national enrolling centres or coordinator. Physicians in Europe who are not officially part of the EC ARVC Consortium and who care for patients with diagnosed or suspected ARVC are strongly encouraged to contact the national enrolling centres or otherwise the ARVC project coordinator and associate coordinators (see anpat.unipd.it/ARVC/ for contact addresses). Regular feedback on Registry results and clinical recommendations will be provided to all enrolling centres.

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