Effect of mental stress on dynamic electrophysiological properties of the endocardium and epicardium in humans

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BACKGROUND Striking temporal associations exist between ventricular arrhythmia and acute mental stress, for example, during natural disasters, or defibrillator shocks associated with stressful events. We hypothesized that electrophysiological changes in response to mental stress may be exaggerated at short coupling intervals and hence relevant to arrhythmia initiation.

OBJECTIVE The aim of this study was to determine the dynamic response in human electrophysiology during mental stress.

METHODS Patients with normal hearts and supraventricular tachycardia underwent electrophysiological studies avoiding sedation. Conditions of relaxation and stress were induced with standardized psychometric protocols (mental arithmetic and anger recall) during decremental S_1S_2 right ventricular (RV) pacing. Unipolar electrograms were acquired simultaneously from the RV endocardium, left ventricular (LV) endocardium (LV endo), and epicardium (LV epi), and activation-recovery intervals (ARIs) computed.

RESULTS Twelve patients (9 women; median age 34 years) were studied. During stress, effective refractory period (ERP) reduced from 228 ± 23 to 221 ± 21 ms ($P < .001$). ARIs reduced during mental stress ($P < .001$), with greater reductions in LV endocardium than in the epicardium or RV endocardium (LV endo −8 ms; LV epi −5 ms; RV endo −4 ms; $P < .001$). Mental stress depressed the entire electrical restitution curve, with minimal effect on slope. A substantial reduction in minimal ARIs on the restitution curve in LV endo occurred, commensurate with the reduction in ERP (LV endo ARI 195 ± 31 ms at rest to 182 ± 32 ms during mental stress; $P < .001$). Dispersion of repolarization increased sharply at coupling intervals approaching ERP during stress but not at rest.

CONCLUSION Mental stress induces significant electrophysiological changes. The increase in dispersion of repolarization at short coupling intervals may be relevant to observed phenomena of arousal-associated arrhythmia.

KEYWORDS Arrhythmia; Mental stress; Restitution; Dispersion of repolarization; Human electrophysiology

ABBREVIATIONS **APD** = action potential duration; **ARI** = activation recovery interval; **ERP** = effective refractory period; **LV** = left ventricular; **RV** = right ventricle/ventricular

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Introduction

The ability of conscious mental activity to influence the risk of cardiac arrhythmia has been well recognized. Controlled data have showed implantable cardioverter-defibrillator shocks to be temporally associated with periods of mental stress.[1,2] In a series of elegant studies, mental stress increased T-wave alternans and decreased arrhythmia threshold in a series of ischemic heart disease patients with implantable cardioverter-defibrillators.[1,3] Furthermore, previous investigators have documented increased arrhythmogenicity in animal models during mental stress.[4] These studies have confirmed a clear link between conscious activity and the risk of arrhythmia, but there are few data documenting the direct effects of such activity on cardiac ventricular electrophysiology.

Taggart et al[5] demonstrated the shortening of the monophasic action potential duration (APD) in human ventricles in response to isoprenaline. A steepening of APD electrical restitution was also observed, which may imply an increased susceptibility to arrhythmia. Recently, our group demonstrated a decrease in the activation recovery interval (ARI; a well-validated surrogate of APD derived from unipolar electrograms) in response to fear independent of heart rate changes.[6] However, dynamic changes in electrophysiology due to mental stress may be even more relevant to the initiation of arrhythmia-clinical arrhythmia often commences with a premature extrasystole. It has been hypothesized that mental stress can contribute to arrhythmia by increasing

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heterogeneity of repolarization and activation (or conduction velocity) throughout the heart. These effects may amplify preexisting heterogeneity especially in the context of ischemic and structural heart disease and thus lead to conduction wavebreak and arrhythmogenesis.

We hypothesized that electrophysiological changes in response to mental stress may become markedly exaggerated at short coupling intervals and hence relevant to arrhythmia initiation by premature beats. This was tested by performing electrophysiological studies on patients with normal ventricles at rest and during a controlled mental stress protocol.

Methods

Catheter placement and clinical studies

The protocol was performed in patients with structurally normal hearts undergoing cardiac electrophysiological studies for the diagnosis and ablation of supraventricular tachycardia. All patients had normal resting electrocardiograms, echocardiograms, and cardiac examinations. The study was approved by the ethics committee of University College London Hospitals (UCL REC no. 10/H7015/19) and conformed to the standards set by the Declaration of Helsinki. All subjects gave prior written informed consent; specifically they were informed that they would be asked to undergo mental arithmetic with firm encouragement and to recall stressful past events as part of the study. Studies were performed with a local anesthetic only in the postabsorptive state. Antiarrhythmic drugs were discontinued for 5 days preprocedure.

Catheters were placed via venous sheaths (6F to 8F), with 4F arterial access (left ventricular [LV] retrograde catheter). All patients received 5000 units of unfractionated heparin. Decapolar catheters were placed in an epicardial coronary vein (great cardiac/middle or lateral vein) via the coronary sinus, retrogradely within the LV cavity adjacent to the epicardial catheter (2-mm electrode spacing, Pathfinder, St Jude Medical Inc, St Paul, MN) and at the right ventricular (RV) apex (2-5-2 mm electrode spacing, Pathfinder; Figure 1). X-ray fluoroscopy was used to guide catheter electrode placement. A reference anodal electrode was placed in the inferior vena cava. Further catheters were placed according to clinical requirements following the research protocol. Electrograms were digitized and recorded at 1000 Hz (Bard Clearsign, CR Bard, NJ, USA, MN). Surface 12-lead electrocardiograms were recorded throughout the study. Oxygen saturations were measured continuously using pulse oximetry, and blood pressure was measured noninvasively at 5-minute intervals. The research study was performed before patients undergoing a clinical electrophysiological study.

Following the clinical procedure, venous and arterial sheaths were removed and hemostasis achieved with manual pressure.

Restitution pacing protocol

A S_1S_2 restitution study was conducted using programmed electrical stimulation. Following 3 minutes of steady-state pacing at the RV apex at a cycle length of 600 ms, a drivetrain of 10 beats was followed by an extrastimulus (S_2). The S_1S_2 interval was decremented by 20–300 ms and thereafter in 5-ms intervals until effective refractory period (ERP) was reached. The ERP was found by increasing coupling intervals (CIs) by 8 ms and then decrementing further by 2-ms intervals.

Mental stress studies

Programmed electrical stimulation was performed during an active relaxation protocol and again during mental stress in the manner described by Burg et al.[7] During active relaxation, subjects were asked to think of a situation that they found subjectively relaxing and were asked to imagine themselves being in that situation. Laboratory lighting was

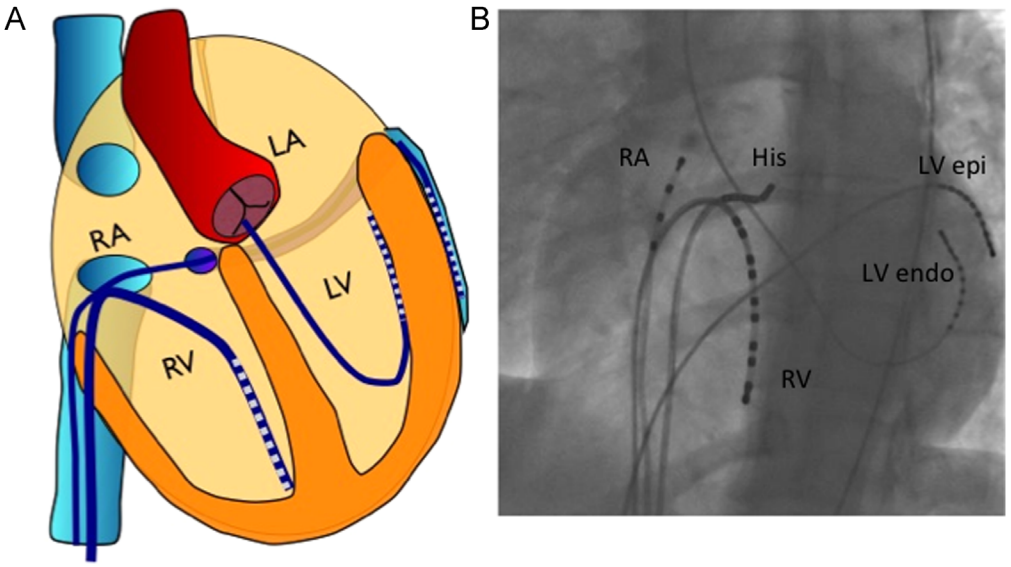

Figure 1 Catheter positions for in vivo studies. Schematic (**A**) and x-ray fluoroscopy (**B**) catheter positions are shown. endo = endocardial; epi = epicardial; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.