Mental stress and emotion have long been associated with ventricular arrhythmias and sudden death in animal models and humans. The effect of mental challenge on ventricular action potential duration (APD) in conscious healthy humans has not been reported.

Methods and Results—Activation recovery intervals measured from unipolar electrograms as a surrogate for APD (n=19) were recorded from right and left ventricular endocardium during steady-state pacing, whilst subjects watched an emotionally charged film clip. To assess the possible modulating role of altered respiration on APD, the subjects then repeated the same breathing pattern they had during the stress, but without the movie clip. Hemodynamic parameters (mean, systolic, and diastolic blood pressure, and rate of pressure increase) and respiration rate increased during the stressful part of the film clip \((P=0.001)\). APD decreased during the stressful parts of the film clip, for example, for global right ventricular activation recovery interval at end of film clip 193.8 ms (SD, 14) versus 198.0 ms (SD, 13) during the matched breathing control (end film left ventricle 199.8 ms [SD, 16] versus control 201.6 ms [SD, 15]; \(P=0.004\)). Respiration rate increased during the stressful part of the film clip (by 2 breaths per minute) and was well matched in the respective control period without any hemodynamic or activation recovery interval changes.

Conclusions—Our results document for the first time direct recordings of the effect of a mental challenge protocol on ventricular APD in conscious humans. The effect of mental challenge on APD was not secondary to emotionally induced altered respiration or heart rate. (Circ Arrhythm Electrophysiol. 2014;7:518-523.)

Key Words: action potentials ■ arrhythmias, cardiac ■ stress, psychological

Clinical Perspective on p 523

Mental stress and emotion are known to strongly influence the pattern of respiration.13–16 The process of breathing has long been known to influence brain stem autonomic neural outflow17 and to affect some aspects of the cardiac electrophysiology. It is well known that mental stress affects both respiration and the autonomic nervous system. However, separating these 2 effects is a challenge experimentally.

The main purpose of this study was to examine the relationship between ventricular APD, respiration, and hemodynamic variables during the viewing of an emotionally charged movie clip during constant rate pacing. We hypothesized that these subjects with normal ventricles would experience changes in hemodynamic indices consistent with enhanced sympathetic activity and may experience small changes in APD. A further aim was to examine the relationship of respiration to APD and hemodynamics during mental stress.
Methods

Studies were performed in 19 subjects (mean age, 57.7; range, 42–75; SD, 8.46 years; 17 men) undergoing cardiac ablation for atrial fibrillation (persistent 3, paroxysmal 16, prior ablation 4). These subjects had normal volumes and ejection fractions assessed by echocardiogram and, despite their atrial fibrillation, were considered to possess healthy ventricles. This study was approved by the Guy’s and St. Thomas’ Hospital Ethics Committee and conformed to the standards set by the Declaration of Helsinki (1996 amendment). Written informed consent was obtained from all subjects. Antiarrhythmic medication was discontinued 5 days before the study. One patient was receiving amiodarone (half-life ≈ 10 to 20 beats per minute above the subject’s intrinsic heart rate, averaging 7 out of 10 on a standardized scale from 0 [no stress] to 10 [maximum possible stress]) and accompanied by an increase in systolic blood pressure (averaging 7 out of 10 on a standardized scale from 0 [no stress] to 10 [maximum possible stress]) and accompanied by an increase in systolic blood pressure of 10 to 15 mm Hg and heart rate of 10 to 15 beats per minute (Taggart P, MD, DSc, unpublished data, 2010), in keeping with most laboratory-based mental stress protocols.21–23 ARIs, as an estimate of APD,24–25 were calculated automatically by the Wyatt method2 (Figure 1) using the algorithm described by Western et al24 from automated custom algorithms using Matlab.

Blood pressure, rate of respiratory pattern on ARI recordings, a novel protocol was used to create a control period in which the subject replicated the same respiratory pattern as the movie period, but in the absence of the psychological stress. This was achieved as follows: After the movie the subjects watched a colored moving ball on the video for a 5-minute relaxation period. During this time, the subjects’ respiration pattern during the movie clip presentation was analyzed. The respiration trace was then played back to the subject via an animated graphical display (implemented in LabVIEW software; National Instruments Corp, Austin, TX); the subject’s variation in chest volume with time was displayed on a moving chart, showing the timing and magnitude of each respiratory cycle as it occurred during the movie clip. A clear indicator highlighted the current state showing inspiration or expiration, and the subjects were further guided by verbal breathing instructions provided by the investigator. A short training period was given before the investigation, and the subject’s compliance was verified during the control period. Mental stress/arousal was solicited by presentation of a short movie clip (4 minutes 30 seconds) depicting a rock-climbing accident (Vertical Limits, Columbia Pictures, 2000). This particular movie clip was chosen because it was perceived to contain a suitable sequence beginning with a minute of low stress, building gradually up to maximum psychological stress at the end. The movie clip had been previously rated by a group of 18 healthy volunteers as moderately stressful (averaging 7 out of 10 on a standardized scale from 0 [no stress] to 10 [maximum possible stress]) and accompanied by an increase in systolic blood pressure of 10 to 15 mm Hg and heart rate of 10 to 15 beats per minute (Taggart P, MD, DSc, unpublished data, 2010), in keeping with most laboratory-based mental stress protocols.21–23 ARIs, as an estimate of APD,24–25 were calculated automatically by the Wyatt method2 (Figure 1) using the algorithm described by Western et al24 from automated custom algorithms using Matlab.

All statistics were performed using SPSS Statistics, version 20 (IBM SPSS, New York). Measurements were recorded during 3

Table 1. Change in Hemodynamic Measurements During the Movie Clip (Low Stress at Start of Movie, High Stress at Mid and End of Movie) and During a Control Period Where the Breathing Pattern at Each Stage Is Repeated Without the Movie

<table>
<thead>
<tr>
<th></th>
<th>Movie</th>
<th>Control</th>
<th>Movie</th>
<th>Control</th>
<th>Movie</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start</td>
<td></td>
<td>Mid</td>
<td></td>
<td>End</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>146.4±20.2</td>
<td>146.5±21.9</td>
<td>153.3±22.3</td>
<td>146.5±21.9</td>
<td>155.3±21.8</td>
<td>144.4±21.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>91.6±12.1</td>
<td>90.4±12.6</td>
<td>94.3±13.2</td>
<td>89.7±12.3</td>
<td>95.6±13.2</td>
<td>90.1±12.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>109.9±13.6</td>
<td>109.0±14.9</td>
<td>114.0±15.2</td>
<td>108.3±14.1</td>
<td>115.5±15.3</td>
<td>108.2±14.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Rate of pressure development, mm Hg/s</td>
<td>1132±485</td>
<td>1173±451</td>
<td>1204±486</td>
<td>1168±447</td>
<td>1218±447</td>
<td>1129±47</td>
<td>0.001</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>15.0±5.9</td>
<td>16.1±5.8</td>
<td>15.7±6.3</td>
<td>16.1±6.2</td>
<td>17.2±5.6</td>
<td>16.8±4.5</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Results are displayed as mean±SD. P values derived from the interaction between movie and time by 2-way ANOVA with repeat measures (via general linear model).
separate 1-minute intervals at start, middle, and end of the movie and control. A 2-way ANOVA with repeat measures (from a general linear model) was used to compare the effects seen during the period of stress (movie) with control (repeat breathing period). Measurements were recorded during 3 separate 1-minute intervals at start, middle, and end of the movie and control.

Results

Hemodynamics
All of the hemodynamic measurements were increased during the high-stress mid and end movie periods, compared with both the low-stress start of movie period and the repeat breathing control period (P=0.001–0.002). For example, systolic blood pressure increased from 146±20 mm Hg at the start of the movie to 153±22 mm Hg and 156±22 mm Hg at the mid and end movie periods, respectively. There was no significant change in hemodynamics comparing the different repeat control periods with different respiration rates (Table 1; Figure 2). The increases in hemodynamic measurements seen during the end movie period compared with the matched breathing control period were systolic blood pressure 11±7 mm Hg, diastolic blood pressure 5±4 mm Hg, mean arterial pressure 7±5 mm Hg, and RPD 89±82 mm Hg per second.

Respiration
As expected, mean respiration rates were similar between the different movie periods and their respective copied breathing control period (Table 1). The average discrepancy between the movie and control period was 0.24±2 breaths per minute. There was a significant increase in the respiration rate seen from the start to the end of the movie (P=0.001).

APD (as Measured by ARI)

Mean Global Change in ARI
Mean values of ARI for the 10 electrodes decreased during the movie compared with the repeat breathing control in both the

Figure 2. Change in hemodynamics and respiration rate between movie and repeat breathing control. The mean change plus 95% confidence intervals is displayed. A, Systolic blood pressure. B, Diastolic blood pressure. C, Rate of pressure development (RPD). D, Respiration rate. The hemodynamic measurement changes significantly increase as the movie sequence becomes more stressful. The increase in respiration rate during the movie is well replicated in the repeat breathing control during mid and end sequence, but not the start.

Figure 3. Change in activation recovery intervals (ARIs) for left (LV) and right ventricles (RV) during the movie clip compared with the matched repeat breathing control. Data are displayed as mean difference compared with breathing control and 95% confidence interval.
left ventricle and right ventricle ($P=0.004$). At the start of the movie, there was little change between control (left ventricle 202.2 ms; right ventricle 197.5 ms) and movie (left ventricle 202.9; right ventricle 195.7 ms). In the mid-movie (left ventricle control 201.2 versus movie 200.1 ms; right ventricle control 197.6 versus movie 194.6 ms) and end-movie (left ventricle control 201.6 versus movie 199.8 ms; right ventricle control 198.0 versus movie 193.8 ms), there was a small but consistent statistically significant shortening of global ARI (Figure 3; Table 2). A similar shortening of ARI is also seen when comparing the movie sequence start (low-stress relaxed sequence) to the high-stress movie mid and end segments ($P<0.001$). This change in ARI is not seen when comparing the different control periods with different repeated breathing rates ($P=0.4$).

**Between-Subject Variability**

There was considerable variability between subjects in the overall mean ARI response. ARI changes in the right ventricle ranged from lengthening by 3.9 ms to shortening by 8.5 ms, and in the left ventricle ranged from lengthening by 2.4 ms to shortening by 12.2 ms. Larger overall changes in ARI were moderately correlated with a greater hemodynamic response (assessed using RPD: right ventricle $r=0.569; P=0.001$; left ventricle $r=0.614; P=0.001$). ARI changes at individual recording sites ranged from lengthening by 7.7 ms to shortening by 15.3 ms.

**Regional Variability**

Similar responses in global ARI shortening were closely correlated between the right and left ventricles ($r=0.78; P<0.001$), that is, super-responders in 1 ventricle showed a similar response in the other ventricle. However, the global degree of ARI shortening during mid/end movie was significantly greater in the right ventricle compared with the left ventricle ($P=0.01$; Figure 2).

Electrode measurements were recorded along the decapolar catheter to assess intraventricular regional variation between the base and apex. Mean ARI shortening at each electrode with 95% confidence interval is shown in Figure 4. Overall there was no significant association between electrode position and degree of ARI shortening ($P=0.5$).

**Discussion**

This study quantified the effect of an emotionally charged movie clip on cardiac repolarization directly from multiple endocardial electrodes in the left and right ventricles, together with central arterial blood pressure, rate of systolic pressure development, and respiration, in conscious cooperative human subjects. As expected, the mild to moderate mental challenge resulted in an increase in mean, systolic, and diastolic blood pressure and RPD. These hemodynamic changes were associated with an overall shortening of ventricular ARI, from which is inferred shortening of APD. The degree of shortening was greater in the right ventricle than in left ventricle. There was no significant variability between the degree of ARI shortening and distal/proximal position of recording electrodes in these patients with relatively normal hearts. The changes in ARI provide direct quantitative evidence for an effect of mental challenge on repolarization, which was previously inferred from skin surface ECG recordings. The QT interval is a global measurement representing the algebraic sum of ventricular APDs and does not provide information on local changes. However, it is local changes in APD that, along with other factors, are a critical component of re-entrant arrhythmias and information on which is essential to understanding and modeling of mechanisms. Furthermore the acquisition of basic electrophysiological data from the in situ hearts of human subjects is important to the current translational approach of interaction between basic science and the clinic.

The mental challenge altered the respiratory pattern. However, the repeated breathing control period demonstrated that the hemodynamic and repolarization changes we observed were not attributable to the alteration in breathing pattern alone, suggesting that these were predominantly generated by the movie-induced psychological stress.

**Methodological Considerations**

The methodology used in this study was novel. The protocol was designed to combine electric recordings from within the heart in conscious subjects undergoing a stressful stimulus unaccompanied by vocalization, which would have interrupted the natural

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**Table 2. Change in Mean ARI During the Movie Compared With the Repeat Breathing Control Period**

<table>
<thead>
<tr>
<th></th>
<th>Start Mean (SD)</th>
<th>Change (95% CI)</th>
<th>Mid Mean (SD)</th>
<th>Change (95% CI)</th>
<th>End Mean (SD)</th>
<th>Change (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle ARI, ms</td>
<td>Movie 203 (17)</td>
<td>0.6 (−0.4, 1.7)</td>
<td>200 (15)</td>
<td>−1.2 (−2.2, −0.1)</td>
<td>200 (16)</td>
<td>−1.8 (−2.8, −0.7)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Control 202 (14)</td>
<td>201 (15)</td>
<td></td>
<td>202 (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricle ARI, ms</td>
<td>Movie 196 (14)</td>
<td>−1.7 (−2.7, −0.7)</td>
<td>195 (14)</td>
<td>−3.0 (−4.0, −2.0)</td>
<td>194 (14)</td>
<td>−4.2 (−5.2, −3.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control 197 (13)</td>
<td>198 (13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean ARI values, SD, and change in ARI (and 95% CI) are shown. ARI indicates activation recovery interval; and CI, confidence interval.
pattern of respiration. We contrived a protocol to enable subjects undergoing routine cardiac catheterization procedures to be shown film clips during the procedure. Film clips are considered to be among the most powerful stimuli to elicit affective responses in the laboratory setting. Film stimuli have several advantages over other stimuli, including their dynamic nature, a sustained effect, and the combination of visual and auditory inputs. The fixed rate pacing protocol allowed us to isolate changes in ARI as a result of psychological stress independent of rate-related effects.

In these studies, we chose systolic blood pressure and the RPD (both of which are validated in this setting) rather than plasma catecholamine sampling as an index of sympathetic activity to better capture short duration changes throughout the protocol and because we had the benefit of high-quality blood pressure signals recorded directly from the central femoral artery.

**Hemodynamic and ARI Changes**

The increase in mean, systolic, and diastolic blood pressure and increase in the rate of RPD during the emotionally charged film clip are consistent with an increase in sympathetic activity. During the movie we observed shortening of APD in both the left and right ventricles in keeping with the known effects of adrenergic stimulation. Experimental work in animal models have reported APD or effective refractory period shortening in the region of 4 to 20 ms compared with 4.5% in the present study. However, the changes reported in response to direct sympathetic nerve manipulation probably relate to the lower intensity of the stimulation caused by the movie we observed shortening of APD in both the left and right ventricles compared with electric nerve stimulation. In support of this notion is the observation that the changes reported in response to direct sympathetic nerve stimulation (4 ms effective refractory period shortening) are analogous to those commonly observed during laboratory stress tasks. It is possible that a more intense mental stress stimulus would have produced more pronounced APD shortening. Several mechanisms could underlie the greater degree of ARI shortening seen in the right ventricle compared with the left ventricle. These include asymmetrical autonomic innervation of the ventricles and asymmetrical central input to the autonomic control system, both of which have been considered to play a possible role in inducing electric heterogeneity and arrhythmogenesis.

The combination of sympathetic stimulation with ischemia is known to enhance dispersion of ventricular repolarization. We would speculate, therefore, that mental challenge exerts only minor effects on ventricular APD in normal hearts but much greater effects in diseased hearts, which is in keeping with previous reports on the ECG repolarization parameters.

Respiration is well known to be influenced by a wide range of stressors from acute psychological threatening stimuli in animals to basic human emotions. In the present study, all subjects demonstrated an increase in respiratory rate during the movie, consistent with other studies on the effect of a mental or emotional challenge. Respiration is known to modulate autonomic activity and alters membrane potentials of preganglionic vagal and sympathetic neurons. Because mental stress is well known to affect both respiration and the autonomic nervous system, it has been uncertain as to their relative roles in mediating the electrophysiological effects of a mental challenge. Our results show that when the altered breathing pattern generated by the movie was copied by the subjects in the absence of the movie, the ventricular APD shortening seen during the movie did not occur. This suggests that the effect of mental challenge on APD was a direct effect via the autonomic nervous system. Several implications may be drawn from our findings. Although APD shortening in response to the mental challenge in these subjects with normal ventricles was a consistent finding, the changes were small and unlikely to pose an arrhythmia risk in themselves. These findings are consistent with the relatively small reported changes in ECG repolarization parameters in response to laboratory stressors in normal subjects. In contrast, studies in humans with coronary artery disease have shown much larger ECG repolarization changes in response to similar laboratory stressors. Furthermore, in animal models of ischemia, large ECG repolarization changes have been observed in response to emotional stress and have been followed by ventricular tachycardia and fibrillation.

**Conclusions**

The present study using mild to moderate mental stress induced by movie clips indicated an effect of the mental challenge on ventricular repolarization, which was inhomogeneous and varied in degree between individuals. Although unlikely to be arrhythmogenic in normal individuals, a more extreme stress or the presence of cardiac pathology may magnify these effects and provide the substrate for ventricular arrhythmias.

**Sources of Funding**

We acknowledge financial support from the Department of Health via the National Institute for Health Research (NIHR) Comprehensive Biomedical Research Centre award to Guy’s and St. Thomas’ NHS Foundation Trust in partnership with King’s College London and King’s College Hospital NHS Foundation Trust. N. Child is funded by an educational fellowship grant from St. Jude Medical. Drs Hanson and Taggart are supported by a grant for the Medical Research Council (grant number G0901819). Dr Bishop is supported by the Centre of Excellence in Medical Engineering funded by the Wellcome Trust and EPSRC under grant number WT088641/Z/09/Z.

**Disclosures**

Dr Gill is in receipt of a nonrelated grant from St. Jude Medical. The other authors report no conflicts.

**References**

Anecdotal reports linking emotional stress with cardiac arrhythmia are common in clinical practice. Human studies in this field have traditionally used ECG-derived parameters to imply an overview of global repolarization parameters. Although this approach is methodologically reproducible, it is unable to identify regional repolarization changes, which are thought to be responsible for arrhythmias. By measuring intracardiac unipolar electrograms during ventricular pacing while subjects watched an emotionally charged movie clip, in this study we were able to demonstrate the changes in local ventricular action potential duration (derived from the activation recovery interval, ARI). We demonstrated, in relatively healthy hearts, that sympathetic stress was associated with small global changes in ARI, and although the degree of ARI shortening was heterogenous between individual subjects, there was little regional variation within an individual ventricle. These effects were independent of any electrophysiological response to changing respiration rates during stress, which are a known confounding factor. Overall, this study shows that in nondiseased hearts ARI shortens in response to stress, but this effect is relatively small and without significant regional variation, meaning the perceived risk of arrhythmia is exceedingly low. How this compares to diseased hearts, where myocardial damage is associated with sympathetic denervation, regrowth, and potential supersensitivity is unknown, but we would predict result in more marked regional ARI variation. A greater physiological understanding of the regional electrophysiological response to sympathetic stress may improve our understanding of cardiac arrhythmia and lead to future treatment options and risk stratification.
Effect of Mental Challenge Induced by Movie Clips on Action Potential Duration in Normal Human Subjects Independent of Heart Rate
Nicholas Child, Ben Hanson, Martin Bishop, Christopher A. Rinaldi, Julian Bostock, David Western, Michael Cooklin, Mark O'Neil, Matthew Wright, Reza Razavi, Jaswinder Gill and Peter Taggart

*Circ Arrhythm Electrophysiol.* 2014;7:518-523; originally published online May 15, 2014; doi: 10.1161/CIRCEP.113.000909

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