# Effects of An Acute Increase in Atrial Pressure on Atrial Refractoriness in Humans

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**CALKINS, H., ET AL.: Effects of An Acute Increase in Atrial Pressure on Atrial Refractoriness in Humans.** *Contraction-excitation feedback has been studied extensively in mammalian ventricles. In contrast, little is known about contraction-excitation feedback in mammalian atria. The objective of this study was to investigate the effect of acute alterations in atrial pressure, induced by varying the atrioventricular (AV) interval, on atrial refractoriness. Twenty patients without structural heart disease participated in the study. In each patient the atrial effective (ERP) and absolute refractory periods (ARP) were measured during AV pacing at a cycle length of 500 msec and an AV interval of 120 msec. Acute increases in atrial pressure were induced by pacing the atrium and ventricle simultaneously for the final two beats of the drive train. The ERP was defined as the longest extrastimulus coupling interval that failed to capture with an extrastimulus current strength of twice the stimulation threshold. The ARP was defined in a similar manner with an extrastimulus current strength of 10 mA. The ERP and ARP were determined using the incremental extrastimulus technique. A subset of patients had the pacing protocol performed during autonomic blockade. As the AV interval of the final two beats of the drive train was shortened from 120 msec to 0 msec, the peak right atrial pressure increased from 7 ± 3 mmHg to 15 ± 5 mmHg ($P < 0.001$). The increase in atrial pressure associated with simultaneous pacing of the atrium and ventricle resulted in shortening of the atrial ERP and ARP by 7.3 ± 5.2 and 6.2 ± 3.5 msec, respectively ($P < 0.001$). Similar results were obtained during autonomic blockade. These findings confirm the presence of contraction-excitation feedback in normal human atria. (PACE, Vol. 15, November, Part I 1992)*

*contraction-excitation feedback, refractoriness, atrioventricular pacing, atrioventricular interval*

## Introduction

Contraction-excitation feedback, the phenomenon whereby changes in mechanics of myocardial contraction precede and result in changes in membrane potential, has been studied extensively in mammalian ventricles.[1–10] These studies have confirmed the presence of contraction-excitation feedback and have also demonstrated the importance of the timing of load alterations in affecting electrophysiological phenomena. In contrast, few studies have investigated contraction-excitation feedback in mammalian atria.[11–13] The results of these studies conflict with each other and/or with the results of prior studies in mammalian ventricles.[1–6] Therefore, it is uncertain whether the phenomenon of contraction-excitation feedback exists in the human atrium.

The purpose of this study was to investigate the phenomenon of contraction-excitation feedback in the human atrium by studying the influence of acute changes in atrial pressure on atrial refractoriness. Atrial pressure was acutely increased by pacing the atrium and ventricle simultaneously for two beats prior to measurement of refractoriness. The effects of an acute increase in atrial pressure on the effective (ERP) and absolute refractory periods (ARP) were evaluated in the baseline state and also during autonomic blockade.

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## Methods

### Subjects Studied

The subjects of this study were 20 patients without underlying structural heart disease who underwent a clinically-indicated electrophysiological test. Seventeen patients had previously undergone radiofrequency catheter ablation of an accessory atrioventricular (AV) connection or modification of the AV node, and the study protocol was performed during a follow-up electrophysiological test. The electrophysiological test in the remaining three patients was performed for evaluation of syncope or paroxysmal supraventricular tachycardia. None of the patients had a history of atrial fibrillation. There were 13 women and 7 men. Their mean age was 36 ± 17 years (± standard deviation). Three additional patients were enrolled in the protocol but were excluded because of the inability to complete the protocol due to the development of sustained atrial fibrillation.

### Electrophysiological Testing

Electrophysiological tests were performed in the fasting, unsedated state at least five half-lives after discontinuation of antiarrhythmic drug therapy including beta blockers and calcium channel blockers. Informed consent was obtained under an investigational protocol approved by the Human Research Committee at the University of Michigan. Three quadripolar electrode catheters were inserted into a femoral vein and positioned in the high right atrium, His-bundle position, and apex of the right ventricle. After completion of the clinically-indicated portion of the electrophysiological test, the electrode catheter in the His-bundle position was replaced with a 6 French multipurpose central lumen catheter, which was positioned in the mid-right atrium for recording atrial pressure. Leads VI, I, and III, the intracardiac electrograms, and the right atrial pressure were recorded on a Siemens-Elema (Solna, Sweden) Mingograf 7 recorder.

### Pacing Protocol

Pacing was performed using a programmable stimulator (Bloom Associates, Reading, PA, USA) with pulses 2 msec in duration and a current intensity twice the stimulation threshold. The atrial stimulation threshold was < 1.5 mA in each subject and the mean stimulation threshold was 0.8 ± 0.3 mA. The ARP and ERP of the right atrium were determined using an AV pacing drive cycle length of 500 msec, a drive train duration of 12 beats, and an intertrain pause of 1 second. The AV interval during the basic drive train was 120 msec. In order to maximize reproducibility of the measurements of refractoriness, the initial beat of the drive train was synchronized to occur 500 msec after a sinus beat and the determinations of the atrial ARP and ERP were preceded by a 3-minute conditioning period during which time basic trains were introduced without the extrastimulus.[14] An atrial extrastimulus was introduced after every 12th atrial paced beat at a coupling interval shorter than the estimated refractory period (typically 160 msec). The coupling interval of the extrastimulus was increased in steps of 2 msec until atrial capture occurred. The ERP was defined as the longest extrastimulus coupling interval that failed to capture the atrium at an extrastimulus current strength of twice the stimulation threshold. The ARP was measured in a similar manner using a drive train current strength of twice diastolic threshold and an extrastimulus current strength of 10 mA.

The ERP and ARP were determined in this fashion in 12 patients, then were measured again following an acute increase in atrial pressure. Acute increases in atrial pressure were induced by shortening the AV relationship of the final two beats of the 12-beat drive train from 120 msec to 0 msec. Finally, the atrial ERP and ARP were measured again at an AV interval of 120 msec to evaluate reproducibility. If atrial fibrillation was induced during determinations of the ERP or ARP, pacing was discontinued until sinus rhythm returned. Data were considered reproducible and acceptable for analysis only if the first and final determinations of the ERP and ARP at an AV interval of 120 msec did not differ by more than 4 msec. If the reproducibility criterion was not met, the measurements were repeated. The ERP was measured because it is used conventionally to measure refractoriness during clinical electrophysiological tests. The ARP was measured because prior studies have demonstrated that the largest effect of

load on refractoriness is detected at high stimulus intensities.[2,3]

### Hemodynamic Measurements

The peak and mean right atrial pressures were recorded during pacing with an AV interval of 120 msec. The peak right atrial pressure of the last beat of the drive train was recorded immediately prior to measurements of refractoriness at each AV interval.

### Autonomic Blockade

To eliminate the possible effects of fluctuations in autonomic tone, the pacing protocol was performed in a second group of eight patients following autonomic blockade. Autonomic blockade was achieved by administration of 0.04 mg/kg of atropine and 0.2 mg/kg of propranolol intravenously over a 10-minute period. The mean dose of propranolol was 13.3 ± 1.9 mg and the mean dose of atropine was 2.6 ± 0.3 mg. Previous studies have demonstrated that these amounts of propranolol and atropine result in complete autonomic blockade.[16] To confirm that the effect of these agents was constant for the duration of the pacing protocol, the sinus rate was measured immediately before and after the pacing protocol was completed. The sinus cycle length immediately following administration of propranolol and atropine but prior to the pacing protocol was no different than at the completion of the pacing protocol (656 ± 51 msec vs 671 ± 59 msec; P = 0.3).

### Statistical Analysis

All data are expressed as mean ± 1 standard deviation. A repeated measures analysis of variance was used to evaluate changes in refractoriness and pressure at differing AV intervals. Differences in the change in refractoriness in the baseline state versus under denervated conditions were compared using the Student's *t*-test. A P value of 0.05 or less was considered significant.

## Results

### Baseline Findings

Table I describes the effects of altering the AV interval on the peak right atrial pressure, atrial ERP, and atrial ARP under baseline conditions. The mean right atrial pressure was 3 ± 2 mmHg during the basic drive train with an AV interval of 120 msec. When the AV interval of the final two beats of the basic drive train was decreased from 120 msec to 0 msec, the peak right atrial pressure increased from 7 ± 3 mmHg to 15 ± 5 mmHg ($P < 0.001$). The atrial ERP measured following two beats of simultaneous pacing of the atrium and ventricle was 7.3 ± 5.2 msec (median = 8, range 0–18, $P < 0.001$) shorter than that measured with an AV interval of 120 msec (Fig. 1). The final atrial ERP, measured with an AV interval of 120 msec to confirm reproducibility, did not differ from the initial measurement of the ERP with an AV interval of 120 msec.

The atrial ARP measured following two beats

**Table I.**

Relationship Between AV Interval, Atrial Pressure, and Atrial Refractoriness

| | AV Interval | | | |
|---|---|---|---|---|
| | 120 msec | 0 msec | 120 msec | P |
| ERP (msec) | 208 ± 19 | 199 ± 21 | 208 ± 19 | <0.001 |
| ARP (msec) | 180 ± 17 | 171 ± 16 | 179 ± 17 | <0.001 |
| RA peak pressure (mmHg) | 7 ± 3 | 15 ± 5 | 7 ± 3 | <0.001 |

Values are expressed as mean ± standard deviation. AV interval = interval between the atrial and ventricular stimulus in the final two beats of the basic drive train; ARP = absolute refractory period; ERP = effective refractory period; RA peak = peak right atrial pressure.

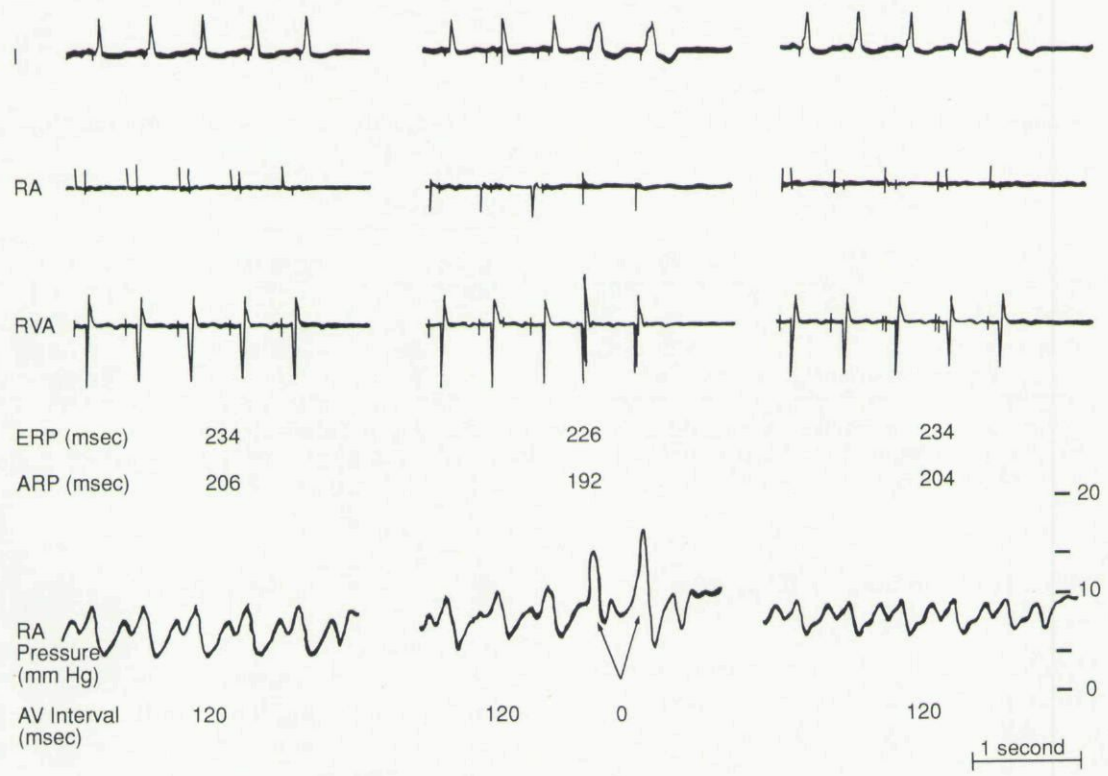


**Figure 1.** *Recording of right atrial pressure during AV pacing with a drive train AV interval of 120 msec and varying AV intervals of the final two beats of the drive train. Shown are surface lead I, and intracardiac electrograms recorded from the right atrium (RA), right ventricular apex (RVA), and the right atrial pressure. The final five beats of the drive train are shown. In the first and third panel, the AV interval is fixed at 120 msec. In the middle panel, the AV interval is 0 msec for the final two beats of the drive train. This shortening of the AV interval results in a marked increase in the peak atrial pressure. Also shown are the atrial effective refractory period (ERP) and absolute refractory period (ARP) that were measured during pacing with each AV interval.*

of simultaneous pacing of the atrium and ventricle was 9.5 ± 5.8 msec (median = 10, range 0–18 msec, $P < 0.001$) shorter than that measured with an AV interval of 120 msec. The final atrial ARP, measured with an AV interval of 120 msec to confirm reproducibility, did not differ from the initial measurement of the ARP with an AV interval of 120 msec.

### Autonomic Blockade

The effects of alterations in the AV interval on the peak right atrial pressure and on the atrial ERP and ARP following pharmacological autonomic blockade are shown in Table II. When the AV interval of the final two beats of the basic drive train decreased from 120 msec to 0 msec, the peak right atrial pressure increased from 8 ± 3 mmHg to 15 ± 5 mmHg ($P < 0.001$). The atrial ERP measured following two beats of simultaneous pacing of the atrium and ventricle was 4 ± 3.7 msec (median = 4, range −2 to 10, $P < 0.001$) shorter than that measured with an AV interval of 120 msec. The atrial ARP measured following two beats of simultaneous pacing of the atrium and ventricle was 6.2 ± 3.5 msec (median = 6, range 0–12 msec, $P < 0.001$) shorter than that measured with an AV interval of 120 msec. The changes in ERP and ARP and the change in peak right atrial pressure induced by shortening of the AV interval were no different than in the baseline state ($P > 0.1$).

**Table II.**

Relationship Between AV Interval, Atrial Pressure, and Refractoriness Following Autonomic Blockade

| | AV Interval | | | |
|---|---|---|---|---|
| | 120 msec | 0 msec | 120 msec | P |
| ERP (msec) | 230 ± 24 | 226 ± 26 | 229 ± 24 | 0.02 |
| ARP (msec) | 202 ± 20 | 196 ± 20 | 201 ± 20 | <0.001 |
| RA peak pressure (mmHg) | 8 ± 3 | 15 ± 3 | 9 ± 3 | <0.001 |

Values are expressed as mean ± standard deviation. AV interval = interval between the atrial and ventricular stimulus in the final two beats of the basic drive train; ARP = absolute refractory period; ERP = effective refractory period; RA peak = peak right atrial pressure.

### Effect of the Site of Ventricular Activation During the Basic Drive Train

During the basic drive train, a variable degree of ventricular fusion was observed between patients at an AV interval of 120 msec. Figure 1 shows ventricular activation occurring primarily via the AV node during the basic drive train. In other patients, minimal fusion was observed during the basic drive train with ventricular activation originating almost entirely from the site of ventricular pacing at the apex of the right ventricle. To evaluate whether the site of ventricular activation influenced the effect of an acute shortening of the AV interval on atrial refractoriness, we compared patients in whom ventricular activation occurred primarily via the AV node (7 patients) with those patients in whom ventricular activation originated primarily from the pacing site (13 patients). In patients in whom conduction occurred primarily via the AV node, the atrial ERP shortened from 223 ± 24 msec to 217 ± 27 msec ($P = 0.001$), and the atrial ARP shortened from 181 ± 19 msec to 171 ± 17 msec ($P < 0.001$) as the AV interval was deceased from 120 msec to 0 msec. Similarly, in the subgroup of patients in whom ventricular activation occurred primarily from the pacing site, the atrial ERP shortened from 205 ± 20 msec to 197 ± 22 msec ($P = 0.02$) and the atrial ARP shortened from 191 ± 22 to 183 ± 24 msec ($P < 0.001$) as the AV interval was decreased from 120 msec to 0 msec. The degree of shortening of the atrial ERP and the atrial ARP was similar in the two groups ($P > 0.1$).

## Discussion

The major finding of this study is that an acute increase in atrial pressure results in shortening of atrial refractoriness. This finding demonstrates that contraction-excitation feedback is present in the human atrium.

### Effects of an Acute Increase in Atrial Pressure on Refractoriness

The results of this study demonstrate that an acute increase in right atrial pressure, induced on a beat-by-beat basis by pacing the atrium and ventricle simultaneously, shortens the atrial ERP and ARP. This finding is consistent with the results of prior experimental studies that demonstrated that acute increases in load applied during the action potential or during systole shorten repolarization. Craelius et al.,[17] for example, characterized stretch sensitive channels in isolated rat myocytes. Activation of these channels by stretch applied during the action potential plateau would result in a repolarizing current. Similarly, in isolated tissue, previous studies[18] have demonstrated that stretch imposed immediately after the onset of the action potential shortens the duration of the action potential. Acute occlusion of the aorta or pulmonary artery in the in situ heart or an acute change from ejecting to isovolumic contraction in the isolated heart has also been shown to shorten repolarization as indexed by the duration of the monophasic action potential (MAP) recording.[5–7]

### Autonomic Blockade

To exclude the possible confounding effects of alterations in sympathetic and vagal tone during pacing at varying AV intervals, the pacing protocol was performed in a second group of eight patients during pharmacological autonomic blockade. The atrial ERP and ARP shortened by a similar degree after simultaneous atrial and ventricular pacing. This provides evidence that the shortening in atrial refractoriness that accompanies an acute rise in atrial pressure is not mediated by a change in sympathetic or vagal tone. These findings are consistent with those of previous experimental studies of contraction-excitation coupling that have demonstrated that the effects of alterations in load are maintained following autonomic blockade.[5,8]

### Abrupt Versus Gradual Changes in Load

No prior study has evaluated that effect of acute changes in atrial pressure on atrial refractoriness. However, a recent study reported the effects on refractoriness of alterations in atrial pressure induced by varying the AV interval under steady-state conditions.[12] A persistent increase in atrial pressure similar to that achieved transiently in this study resulted in no change in the atrial ERP and ARP. The disparate findings of these two studies are consistent with the current understanding of contraction-excitation feedback and confirm the importance of the time course of load change. In isolated tissues, for example, several studies have shown that gradual changes in load have little effect on the action potential.[19–21] In contrast, abrupt stretch imposed for a single beat immediately following onset of depolarization results in shortening of the action potential duration.[18] The time course of load change has also been shown to be important in intact ventricles. Under steady-state conditions, > 100% increases in ventricular volume have been shown to result in only slight (< 1%) shortening of refractoriness and no change in repolarization as indexed by MAP recordings.[1,4] In contrast, a sudden increase in load induced by acute occlusion of the aorta shortens the duration of repolarization as indexed by MAP recordings.[5]

### Limitations

A limitation of this study is that noninvasive determination of right atrial volumes was technically not possible and, therefore, the change in right atrial wall stress could not be determined. Although atrial size was not measured in this study, previous studies have demonstrated that the left atrial size increases as the AV interval during pacing is decreased from 160 msec to 0 msec.[11] From this observation, we presume that right atrial size increased as the AV interval was shortened and the right atrial pressure increased.

### Conclusions

The results of this study demonstrate that abrupt increases in atrial pressure induced on a beat-by-beat basis shorten refractoriness. These findings confirm the presence of contraction-excitation feedback in the normal human atrium. The effect of acute changes in atrial pressure on refractoriness in structurally abnormal atria and the clinical importance of contraction-excitation feedback in the development of atrial arrhythmias remain to be determined.

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