Br Heart J 1994;71:34–37

Differential effect of pharmacological autonomic blockade on some electrophysiological properties of the human ventricle and atrium*

Wataru Shimizu, Yukiko Tsuchioka, Shinji Karakawa, Kenji Nagata, Junko Mukai, Togo Yamagata, Hideo Matsuura, Goro Kajiyama, Yuichiro Matsuura

Abstract

***Objective*—This study investigated the dominance of each limb of the autonomic nervous system and tested sympathetic-vagal interactions in the human ventricle and atrium after administration of propranolol and atropine.**

***Patients and methods*—The 90% monophasic action potential duration (MAPD90) and the effective refractory period (ERP) at the right ventricular apex (RV) and the right lateral atrium (RA) were measured in 14 patients. The MAPD90 was measured during constant RV and RA pacing (cycle length 600 ms) and the ERP was measured at a driven cycle length of 600 ms. Electrophysiological variables were measured during a control period, after propranolol (0·15 mg/kg loading dose followed by 0·1 mg/min infusion), and after autonomic blockade (atropine 0·04 mg/kg).**

***Results*—Both RV MAPD90 and RV ERP increased after propranolol (RV MAPD90 from 268 (26) ms to 275 (26) ms, $p < 0·005$; RV ERP from 252 (25) ms to 258 (26) ms, $p < 0·0005$) and then decreased to below the control values after autonomic blockade (RV MAPD90 256 (24) ms; RV ERP 239 (25) ms, $p < 0·0005$ *v* propranolol, $p < 0·0005$ *v* control). In contrast, both RA MAPD90 and RA ERP increased after propranolol (RA MAPD90 from 242 (19) ms to 260 (19) ms; RA ERP from 216 (21) ms to 230 (18) ms, $p < 0·0005$), and then increased slightly more after autonomic blockade (RA MAPD90 265 (16) ms, $p = 0·09$; RA ERP 235 (16) ms, $p = 0·07$), thus remaining above control values ($p < 0·0005$).**

***Conclusions*—The results indicate (a) that in the human ventricle vagal stimulation and sympathetic β stimulation are antagonistic and that direct vagal stimulation predominates over β stimulation, with sympathetic-vagal interaction being minimal and (b) that in the human atrium vagal stimulation and β stimulation are synergistic and β stimulation predominates over vagal stimulation, with direct vagal stimulation having a minimal effect.**

(*Br Heart J* 1994;71:34–37)

Both limbs of the autonomic nervous system (sympathetic and parasympathetic) can influence cardiac electrophysiological properties: each limb predominates in different areas of the heart and over different electrophysiological properties. Vagal stimulation predominates over sympathetic stimulation in the human sinus node, whereas both limbs have a balanced effect on the function of the atrioventricular node.[1] Prystowsky *et al* suggested that vagal stimulation and sympathetic stimulation are antagonistic in the human ventricle and that vagal stimulation is dominant over sympathetic stimulation in terms of influence on resting ventricular refractoriness.[2] In contrast, that vagal stimulation and sympathetic stimulation (β stimulation) were reported to be synergistic in the human atrium[3] though their relative dominance in this part of the heart has not yet been fully defined. Furthermore, both limbs of the autonomic nervous system are known to interact with each other so that the vagal effect on cardiac electrophysiological properties becomes more pronounced as the level of resting sympathetic tone increases (sympathetic-vagal interaction).[1 4] In the present study we assessed the relative dominance of both limbs of the autonomic nervous system in terms of action potential duration and refractoriness in the human ventricle and atrium and investigated sympathetic-vagal interactions by using propranolol and atropine to produce pharmacological autonomic blockade.

Patients and methods

We studied 14 patients (table) in sinus rhythm who were undergoing electrophysiological studies. The diagnosis was Wolff-Parkinson-White syndrome in six patients (one manifest and five concealed), idiopathic ventricular premature contractions in four patients, second degree atrioventricular block in three patients, and syncope of unknown origin in one patient. There were six men and eight women aged from 18 to 73 years (mean (SD) 46 (17) years). Patients were excluded if they had sick sinus syndrome, atrial fibrillation, ischaemic heart disease, congestive heart failure, uncontrolled hypertension (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >95 mm Hg), if they had had cardiac surgery within the previous two

First Department of Internal Medicine Hiroshima University School of Medicine, Japan
W Shimizu
Y Tsuchioka
S Karakawa
K Nagata
J Mukai
T Yamagata
H Matsuura
G Kajiyama

First Department of Surgery
Y Matsuura

Correspondence to
Dr Wataru Shimizu, Division of Cardiology, National Cardiovascular Centre, 5-7-1 Fujishiro-dai, Suita, Osaka, Japan, 565.

Accepted for publication 26 July 1993.

*The study was presented in part at the NASPE 13th Annual Scientific Sessions, Chicago, Illinois, USA, 16 May 1992.

Clinical characteristics of the 14 patients

Case	*Age*	*Sex*	*Diagnosis*
1	52	F	II AVB
2	42	F	WPW(C)
3	55	F	II AVB
4	51	M	WPW(M)
5	64	M	Idp VPC
6	73	M	Idp VPC
7	56	M	WPW(C)
8	56	F	WPW(C)
9	18	M	II AVB
10	23	F	Syncope
11	58	M	WPW(C)
12	29	F	Idp VPC
13	26	F	Idp VPC
14	43	F	WPW(C)

Idp VPC, idiopathic ventricular premature contractions; IIA VB, second degree AV block; WPW (C), concealed Wolff-Parkinson-White syndrome; WPW(M), manifest WPW syndrome.

months, or if they had any other contraindications to pharmacological autonomic blockade.

ELECTROPHYSIOLOGICAL STUDY

Written informed consent was obtained from all subjects and they were investigated in a nonsedated, postabsorptive state after all antiarrhythmic medications had been stopped for at least five drug half-lives.

Two 6F or 7F monophasic action potential (MAP) catheters (EP Technologies pacing-MAP recording combination catheters) were introduced through a femoral vein and advanced into the right ventricular apex (RV) and the right lateral atrium (RA) under fluoroscopic guidance.

SIMULTANEOUS PACING AND MAP RECORDING

Simultaneous pacing and MAP recording were performed by the contact electrode technique as described elsewhere.[5-7] MAP signals were amplified with a direct-current-coupled, differentiated preamplifier (model 1001, EP Technologies) at a frequency of 0–5000 Hz. The MAP signals, six surface electrocardiographic leads, and the femoral arterial pressure trace were all displayed simultaneously on a strip chart recorder (Siemens-Elema, 16 channel Mingograf) at paper speeds of 100 and 200 mm/s. RV and RA pacing at a constant cycle length (CL) of 600 ms was performed for at least 3 min via the pacing bipole of the MAP catheter using 2 ms rectangular stimuli at twice diastolic threshold. MAP signals were simultaneously recorded with the same catheter. The RV MAP duration during constant RV pacing and the RA MAP duration during constant RA pacing were determined at 90% repolarisation (MAPD90) and averaged for at least three beats. Then RV and RA extrastimuli were delivered to the same sites through the same MAP catheter. A single extrastimulus (S2) was introduced in 5–10 ms steps after every eighth driven stimulus at a CL of 600 ms. The RV and RA effective refractory periods (ERPs) were defined as the longest RV and RA coupling intervals (S1S2) at which S2 did not achieve capture.

PROTOCOL

After the control electrophysiological variables were measured a loading dose of propranolol (0·15 mg/kg at 1 mg/min) was followed by continuous propranolol infusion at 0·1 mg/min. Electrophysiological data were obtained 5 min after infusion of the loading dose of propranolol. Then atropine (0·04 mg/kg) was infused for 5 min, and the electrophysiological data during autonomic blockade were measured 5 min after the atropine infusion.

STATISTICAL ANALYSIS

Results are mean (SD). Student's t test for paired data was used to compare measurements made before and after drug administration, and a p value of $< 0·05$ was regarded as significant.

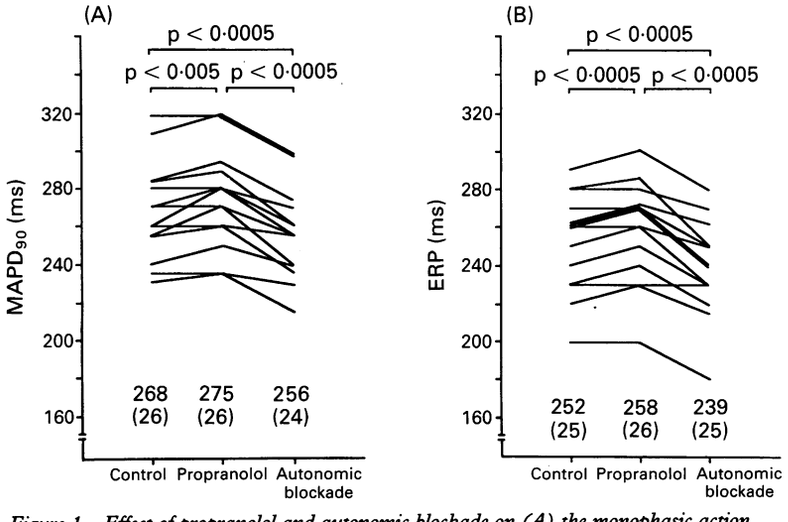

Figure 1 Effect of propranolol and autonomic blockade on (A) the monophasic action potential duration at 90% repolarisation (MAPD90) and (B) the effective refractory period (ERP) in the ventricle.

Results

The sinus CL increased significantly from 890 (129) ms to 1009 (111) ms after propranolol ($n = 14$, $p < 0·0005$) and then decreased to significantly less than the control value (711 (83) ms) after the additional administration of atropine (autonomic blockade) ($n = 14$, $p < 0·0005$ v after propranolol, $p < 0·001$ v control). RV MAPD90 increased significantly from 268(26) ms to 275(26) ms after propranolol ($n = 14$, $p < 0·005$) and then decreased to significantly less than the control value after autonomic blockade (256(24) ms) ($n = 14$, $p < 0·0005$ v after propranolol, $p < 0·0005$ v control) (fig 1A). Similarly, the RV ERP increased significantly from 252(25) ms to 258(26) ms after propranolol ($n = 14$, $p < 0·0005$), and then decreased to significantly less than the control value after autonomic blockade (239(25) ms ($n = 14$, $p < 0·0005$ v after propranolol, $p < 0·0005$ v control) (fig 1B). In contrast, the RA MAPD90 increased significantly from 242(19) ms to 260(19) ms after propranolol ($n = 14$, $p < 0·0005$) and then increased slightly to 265(16) ms after autonomic

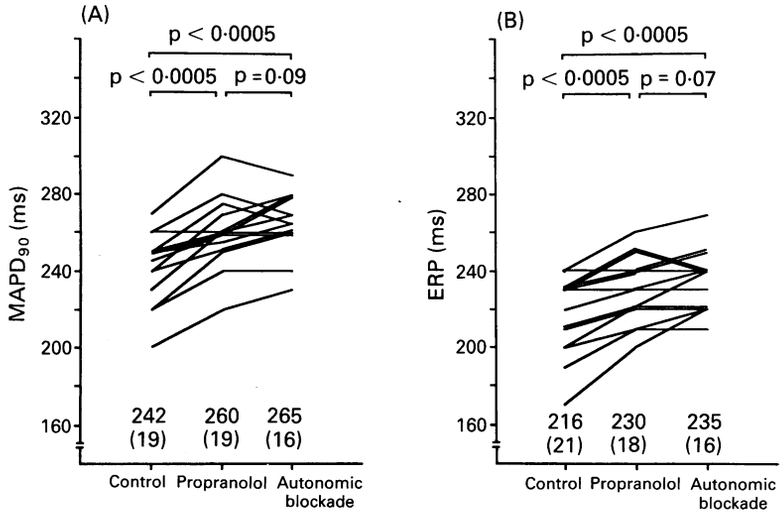

Figure 2 Effect of propranolol and autonomic blockade on (A) the monophasic action potential duration at 90% repolarisation (MAPD90) and (B) the effective refractory period (ERP) in the atrium.

blockade (n = 14, p = 0·09). Therefore, the overall effect of autonomic blockade was to increase the RA MAPD90 from the control level (n = 14, p < 0·0005) (fig 2A). Similarly, the RA ERP increased significantly from 216(21) ms to 230(18) ms after propranolol (n = 14, p < 0·0005) and then increased slightly to 235(16) ms after autonomic blockade (n = 14, p = 0·07), so the overall effect of autonomic blockade was again to cause an increase from the control value (n = 14, p < 0·0005) (fig 2B).

Mean arterial pressure during constant RA pacing (CL 600 ms) did not change between the control state, after propranolol, and after autonomic blockade (n = 14, 101(16) mm Hg *v* 101(17) mm Hg *v* 102(18) mm Hg). Figures 3 and 4 show a representative example of the effects of propranolol and autonomic blockade on the RV and RA MAPD90 (case 4).

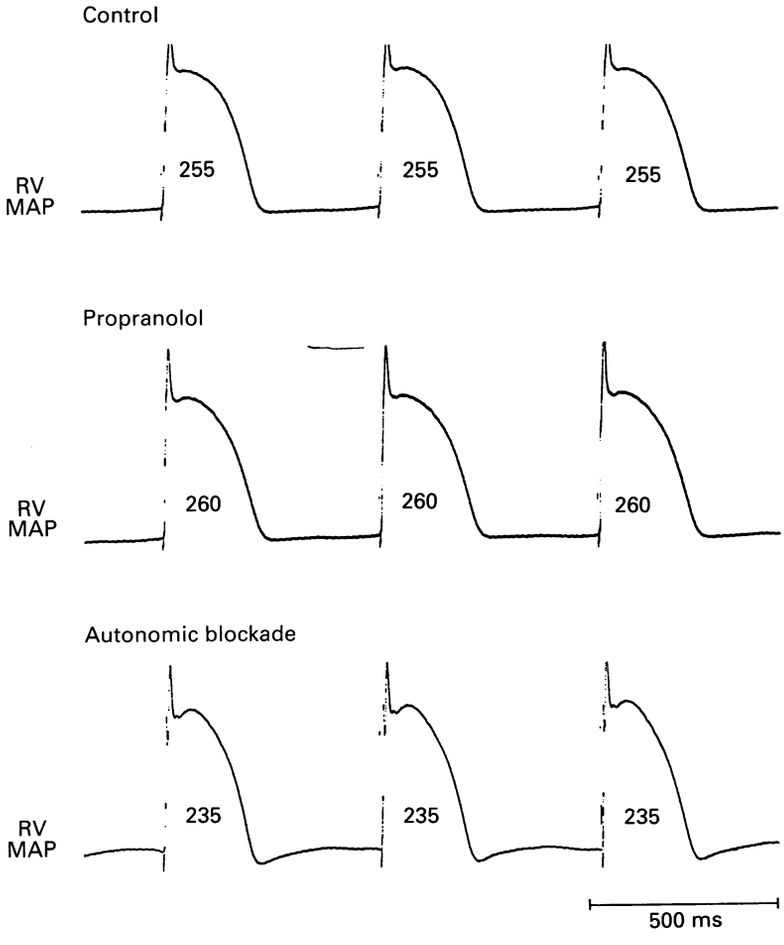

Figure 3 Recordings of monophasic action potential (MAP) made at the right ventricular apex (RV MAP) in the control state (upper panel), after propranolol administration (middle panel), and after autonomic blockade (lower panel) during constant RV pacing (CL 600 ms). The RV MAP duration at 90% repolarisation (MAPD90) increased from 255 to 260 ms after propranolol and then decreased to below the control value (235 ms) after autonomic blockade.

Discussion

EFFECTS OF THE AUTONOMIC NERVOUS SYSTEM ON THE HUMAN VENTRICLE

Sympathetic stimulation and adrenaline decreased the action potential duration (APD) and the ERP of the ventricle in both experimental[8 9] and human studies.[10] Whereas in animal[8 11] and human studies in vivo[12] the ERP of the ventricle clearly increased in response to vagal stimulation or acetycholine (a vagal agonist). Thus it was suggested that vagal stimulation and sympathetic (β) stimulation are antagonistic in the animal and human ventricle in vivo. In contrast, the effects of acetylcholine on the APD of the Purkinje fibres in different animal species in vitro varied widely.[13] These differences in studies of vagal effects in vivo and in vitro have generally been explained on the basis of sympathetic-vagal interaction—that is, by accentuated vagal antagonism of sympathetic effects after an increase in sympathetic tone.[1 4 9] However, Prystowsky *et al* suggested that vagal stimulation does not require a background sympathetic tone to exert its effect on the human ventricle, because atropine decreases the ERP of the ventricle even after preadministration of propranolol.[2] In contrast, Morady *et al* suggested that a certain level of sympathetic tone was required for accentuated antagonism to occur in the human ventricle.[14]

In the present study, propranolol significantly increased both the RV MAPD90 and the RV ERP, while the additional administration of atropine significantly decreased these variables to below the control values. These results accord with those of Prystowsky *et al.*[2] They suggest that vagal stimulation and β stimulation are antagonistic, that sympathetic-vagal interaction is minimal, and that the effect of direct vagal stimulation (increasing refractoriness) predominates over that of β stimulation in the human ventricle.

EFFECTS OF THE AUTONOMIC NERVOUS SYSTEM ON THE HUMAN ATRIUM

Several studies have suggested that isoproterenol (β stimulation) and adrenaline (both β and α stimulation) can decrease the ERP of the atrium as well as the ERP of the ventricle in humans.[10] Similarly, vagal stimulation and acetylcholine have been reported to decrease

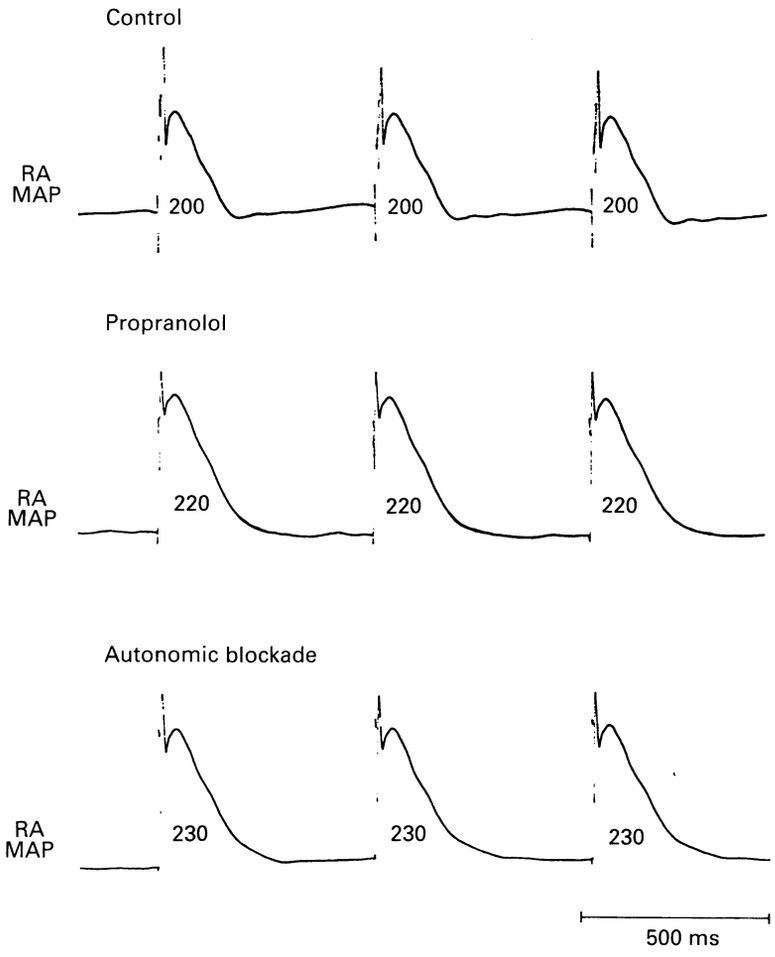

Figure 4 Recordings of monophasic action potential (MAP) made at the right lateral atrium (RA MAP) in the control state (upper panel), after propranolol administration (middle panel), and after autonomic blockade (lower panel) during constant RA pacing (CL 600 ms). The RA MAP duration at 90% repolarisation (MAPD90) increased from 200 to 220 ms after propranolol and then increased slightly to 230 ms after autonomic blockade.

the APD and ERP of the atrium in in vivo and in vitro studies by increasing the acetylcholine-activated K^+ current that is found in the atrium but not in the ventricle.[15 16] Furthermore, Prystowsky *et al* reported that enhanced vagal tone (produced by neck suction) decreased the ERP in the human atrium.[3] Thus it seems that vagal stimulation and β stimulation may be synergistic in the human atrium. On the other hand, several recent experimental studies have suggested that α stimulation could increase the ERP of the atrium and be antagonistic to both vagal and β stimulation.

We found that propranolol significantly increased both the RA MAPD90 and the RA ERP and that the addition of atropine further increased these variables. The difference between propranolol alone and autonomic blockade was not statistically significant, however. These results indicate that vagal stimulation and β stimulation are synergistic and that the effect of β stimulation predominates over that of direct vagal stimulation in the human atrium: we could not obtain total autonomic blockade in our patients because α stimulation was still present.

1 Levy MN, Zieske H. Autonomic control of cardiac pacemaker activity and atrioventricular transmission. *J Appl Physiol* 1969;**27**:465–70.
2 Prystowsky EN, Jackman WM, Rinkenberger RL, Heger JJ, Zipes DP. Effects of autonomic blockade on ventricular refractoriness and atrioventricular nodal conduction in humans: evidence supporting a direct cholinergic action on ventricular muscle refractoriness. *Circ Res* 1981;**49**:511–8.
3 Prystowsky EN, Naccarelli GV, Jackman WM, Rinkenberger RL, Heger JJ, Zipes DP. Enhanced parasympathetic tone shortens atrial refractoriness in man. *Am J Cardiol* 1983;**51**:96–100.
4 Levy MN. Sympathetic-parasympathetic interactions in the heart. *Circ Res* 1971;**29**:437–45.
5 Franz MR. Long-term recording of monophasic action potentials from human endocardium. *Am J Cardiol* 1983;**51**:1629–34.
6 Franz MR, Chin MC, Sharkey HR, Griffin JC, Scheinman MM. A new single catheter technique for simultaneous measurement of action potential duration and refractory period in vivo. *J Am Coll Cardiol* 1990;**16**:878–86.
7 Shimizu W, Ohe T, Kurita T, Takaki H, Aihara N, Kamakura S, *et al*. Early afterdepolarizations induced by isoproterenol in patients with congenital long QT syndrome. *Circulation* 1991;**84**:1915–23.
8 Martins JB, Zipes DP. Effects of sympathetic and vagal nerves on recovery properties of the endocardium and epicardium of the canine left ventricle. *Circ Res* 1980;**46**:100–10.
9 Nattel S, Euler DE, Spear JF, Moore EN. Autonomic control of ventricular refractoriness. *Am J Physiol* 1981;**241**(suppl H):878–82.
10 Morady F, Nelson S, Kou WH, Pratley R, Schmaltz S, Buitleir MD, Halter JB. Electrophysiologic effects of epinephrine in humans. *J Am Coll Cardiol* 1988;**11**: 1235–44.
11 Inoue H, Zipes DP. Changes in atrial and ventricular refractoriness and in atrioventricular nodal conduction produced by combinations of vagal and sympathetic stimulation that result in a constant spontaneous sinus cycle length. *Circ Res* 1987;**60**:942–51.
12 Ellenbogen KA, Smith ML, Eckberg DL. Increased vagal cardiac nerve traffic prolongs ventricular refractoriness in patients undergoing electrophysiology testing. *Am J Cardiol* 1990;**65**:1345–50.
13 Gilmour RF, Zipes DP. Positive inotropic effects of acetylcholine in canine cardiac Purkinje fibers. *Am J Physiol* 1985;**249**(suppl H):735–40.
14 Morady F, Kou WH, Nelson SD, Buitleir ND, Schmaltz S, Kadish AH, *et al*. Accentuated antagonism between β-adrenergic and vagal effects on ventricular refractoriness in humans. *Circulation* 1988;77:289–97.
15 Zipes DP, Mihalick MJ, Robbins GT. Effects of selective vagal and stellate ganglion stimulation on atrial refractoriness. *Cardiovasc Res* 1974;**8**:647–55.
16 Iijima T, Irisawa H, Kameyama M. Membrane currents and their modification by acetylcholine in isolated single atrial cells of the guinea-pig. *J Physiol* 1985;**359**: 485–501.