EFFECT OF PACING RATE AND β_1-BLOCKADE ON CARDIAC REFRACTORY PERIODS AND HIS-BUNDLE CONDUCTION

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Abstract

Stimulation of the sympathetic nervous system releases norepinephrine, activating beta receptors and triggering increases in heart rate (HR) and atrioventricular (AV) conduction velocity. Metoprolol is a selective beta receptor blocker, which causes a decrease in sinus HR and slows AV conduction. The purpose of this study was to assess the effects of pacing and beta blockade on cardiac electrophysiologic parameters in the anesthetized dog. Two bipolar plunge electrodes were used to determine atrial and ventricular refractory periods (AERP and VERP), as well as to record atrial electrograms. A multipolar electrophysiology catheter positioned distal to the bicuspid valve was used to record His bundle electrograms to determine atria to His (AH) and His to ventricle (HV) interval measurements. The AV nodal refractory period (AVNERP) was also calculated. In nontreated dogs (n=11), AVNERP and AH intervals were prolonged at 180 bpm compared to 120 bpm (AVNERP: 201±17 vs. 192±18 msec and AH: 128±6 vs. 119±5 msec, respectively). Atrial ERP, VERP and HV intervals were similar when hearts were paced at 120 and 180 bpm. Treatment with 0.1, 0.3 and 1.0 mg/kg metoprolol dose-dependently decreased sinus HR (10 to 20% from baseline) and increased AVNERP (10 to 25% from baseline) with 180 or 120 bpm pacing. Metoprolol also prolonged AH conduction time. In conclusion, increasing pacing rate prolongs AVNERP and AH conduction time. In contrast, beta blockade decreases HR, but also increases AH interval, suggesting slowing of supraventricular conduction.

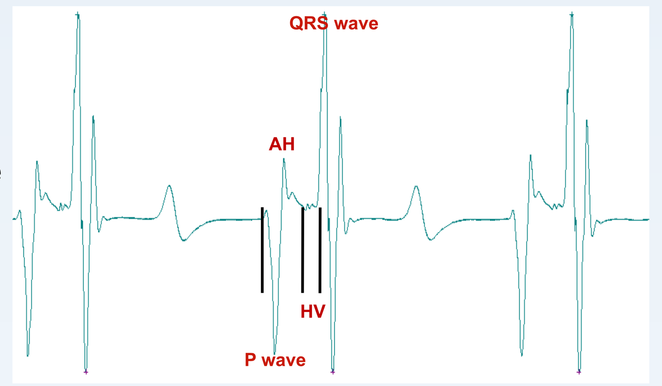
Methods

Male Beagle dogs (6-14 months old; 7-14 kg) were anesthetized for intubation with intravenous Propofol (5-6 mg/kg). After intubation, dogs were placed on isoflurane gas anesthesia which was maintained at 1.5 - 2.5% with 1- 2 L/min of 100% oxygen. Morphine (0.5mg/kg) was used in addition for pain management in this open chest procedure. Dogs were placed on a heating pad set to maintain the animal's body temperature at approximately 37ºC.

An incision was made between the 2nd and 3rd or the 3rd and 4th ribs to visualize the heart. The heart was isolated and two bipolar plunge electrodes were sutured to the epicardial right ventricular outflow tract and two were sutured near the left atrial appendage. The atrial and ventricular electrodes were used for the measurement of atrial and ventricular refractory periods (AERP and VERP) as well as to record atrial electrograms.

A solid-state high fidelity pressure catheter (Millar Instruments) for arterial pressure monitoring purposes was inserted into a carotid artery and secured with suture. A multipolar (Bard Electrophysiology) electrophysiology catheter was positioned distal to the bicuspid valve via the femoral artery to record His bundle electrograms to determine AH (atrial to His) and HV (His to ventricle) interval measurements.

Diagram of His Bundle Electrogram



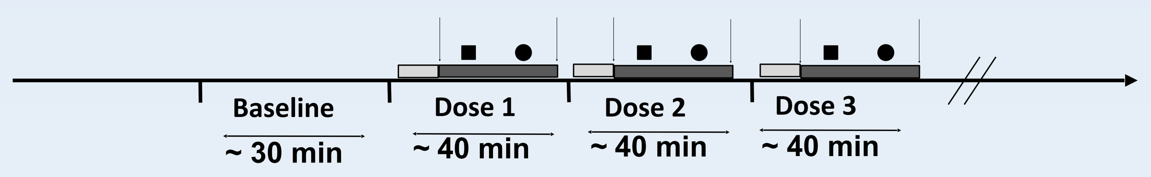
Electrophysiologic Determinations

All determinations were conducted and reported at 2 decremental cycle lengths (500 msec (120 bpm) and 333 msec (180 bpm) using either atrial or ventricular pacing as appropriate. Pacing was conducted for 60 seconds, before electrophysiologic parameters are measured. For determination of atrial effective refractory period (AERP), hearts experienced cycles of 8 paced beats (A_1) of atrial origin (s1: at twice electrical diastolic threshold, fixed cycle length) followed by an extra atrial stimulus (s2) delivered at varying coupling intervals from the eight beat train of s1 initiating immediately following dosing. The coupling time that failed to elicit an s2 stimulus derived atrial beat (A_2) was noted as the AERP.

For determination of ventricular effective refractory period (VERP), hearts experienced constant ventricular pacing (s1: at twice electrical diastolic threshold, fixed cycle length). Extra ventricular stimuli (s2) was delivered at varying coupling intervals from the constant s1 initiating just after the completion of each AERP determination. The coupling interval that failed to elicit an extrasystole was noted as the VERP.

For determinations of atrioventricular nodal effective refractoriness (AVNERP), hearts experienced cycles of 8 paced beats of atrial origin (s1: at twice electrical diastolic threshold, fixed cycle length) followed by an extra atrial stimulus (s2) delivered at varying coupling intervals from the 8 beat train of s1 initiating immediately following dosing. The coupling time that failed to elicit an s2 derived ventricular beat was noted as the AVNERP.

Protocol



■ Record hemodynamic (HR and aortic pressures) and all electrophysiology parameters (AERP, AVNERP, VERP, PA, AH, HV, PR, QRS, QT, QTc) at 500 msec

● Record hemodynamic (HR and aortic pressures) and all electrophysiology parameters (AERP, AVNERP, VERP, PA, AH, HV, PR, QRS, QT, QTc) at 333 msec

| Record hemodynamic (HR and aortic pressures) and AH, HV, PR, QRS, QT, QTc at sinus rhythm (at the end of loading dose and at the end of the maintenance dose)

Loading dose

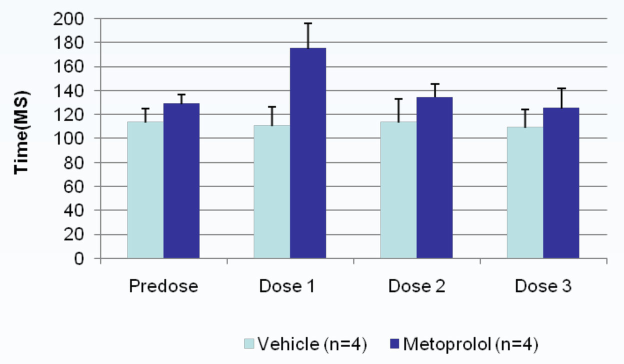
Maintenance dose

Metoprolol doses 1, 2, and 3 are 0.1, 0.3 and 1.0 mg/kg respectively; vehicle (5% Dextrose) was administered at corresponding volumes

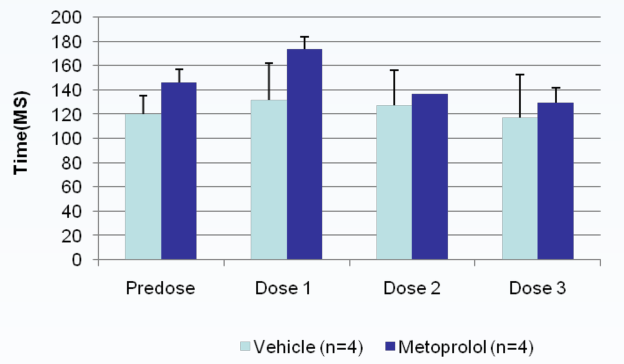
Results

- 0.1, 0.3 and 1.0 mg/kg metoprolol decreased sinus heart rate 10-20% compared to vehicle treated dogs

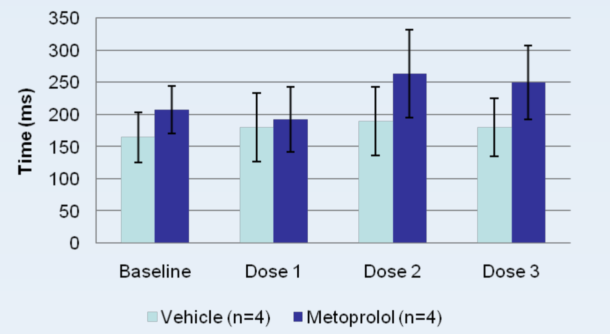
AH at 500 msec



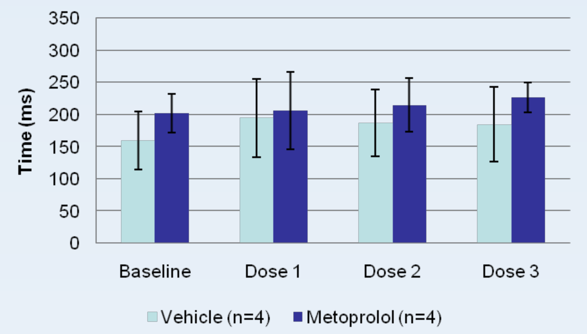
AH at 333 msec



AVNERP at 500 msec



AVNERP at 333 msec



His Bundle and ERP Measurements in Vehicle and Metoprolol Treated Dogs

	CL	Vehicle(n=11)	0.1 mg/kg(n=4)	0.3 mg/kg(n=4)	1.0 mg/kg(n=4)
A-H (msec)					
	Sinus	96±6	107±11	106±16	100±15
	500 msec	119± 5	175±21	134±11	125±16
	333 msec	128±6	174±10	137±0	130±12
H-V (msec)					
	Sinus	23±1	26±2	28±2	27±1
	500 msec	24±1	28±1	29±0	27±1
	333 msec	23±1	28±1	29±0	27±1
AERP (msec)					
	500 msec	100±6	91±17	108±19	108±8
	333 msec	99±6	100±11	103±17	103±9
VERP (msec)					
	500 msec	141±7	170±3	165±8	168±4
	333 msec	141±6	152±6	153±6	150±7
AVNERP (msec)					
	500 msec	192±18	193±50	263±68	250±58
	333 msec	201±17	206±60	215±41	227±23

Conclusion

- **In non-treated animals, increases in heart rate prolong AVNERP and A-H conduction times, which reflect the changes in cardiac electrophysiology when the heart is stimulated.**

- **Metoprolol dose-dependently decreases HR and AV conduction. An increase in A-H interval suggest slowing of supraventricular conduction.**

- **The anesthetized dog is a suitable model for determination of the effects of pacing and pharmacologic intervention on cardiac refractory periods and His bundle conduction**