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普罗帕酮对麻醉兔左心室后负荷变化引起的电生理改变的影响

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Effects of propafenone on electrophysiologic changes caused by alteration of left ventricular afterload in anesthetized rabbits

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KEY WORDS left ventricular dysfunction; ventricular outflow obstruction; ventricular pressure; electrophysiology; ventricular fibrillation; propafenone; nitroprusside

AIM: To study effects of propafenone (Pro) on ventricular electrophysiologic changes caused by alteration of left ventricular afterload of rabbit heart. **METHODS**: Before and after iv Pro 3 mg·kg^{-1}, changing afterload of left ventricle (LV), occurrence of ventricular arrhythmia, left ventricular diastolic thresholds (VDT), relative refractory period (RRP), effective refractory period (ERP), dispersion of refractory period, and ventricular fibrillation threshold (VFT) were recorded. **RESULTS**: Increasing afterload of LV increased temporal dispersion of RRP and ERP [from 11 ± 4 and 6 ± 3 ms to 18 ± 8 and 13 ± 8 ms (+ ΔP = 8.4 ± 2.9 kPa) individually ($P < 0.05$)] and decreased VFT [from 5.5 ± 1.0 V to 3.9 ± 0.9 V ($P < 0.01$)]; Ventricular arrhythmia was seen in all rabbits. But reducing left ventricular afterload did not alter the electrophysiologic parameters in LV and did not induce ventricular arrhythmia. Pro iv prolonged RRP and ERP, increased VDT and VFT ($P < 0.01$); Increasing or decreasing left ventricular afterload did not cause much alteration of ventricular electrophysiologic parameters ($P > 0.05$). **CONCLUSION**: Pro inhibited increase of dispersion of refractory period and decrease of VFT caused by increase of left ventricular afterload and has an effect of anti-ventricular arrhythmia.

关键词 左室功能障碍；心室流出道梗阻；心室压力；电生理学；心室纤颤；普罗帕酮；硝普盐

目的：探讨普罗帕酮（Pro）对兔左心室后负荷变化引起的心室电生理改变的作用. **方法**：Pro 3 mg·kg^{-1} iv 前后，改变左心室后负荷，观察室性心律失常发生情况；并测定左心室舒张阈值（VDT），相对不应期（RRP），有效不应期（ERP）及其不应期离散和心室纤颤阈（VFT）. **结果**：增加左心室后负荷（B 级），可使左室 RRP 和 ERP 时间离散增加，VFT 降低，并出现室性心律失常. Pro iv 后，VDT，RRP，ERP，VFT 均较用药前显著延长或升高（$P < 0.01$）；改变左室后负荷，心室电生理参数无显著改变（$P > 0.05$）. **结论**：Pro 可抑制左室后负荷增加引起的不应期离散增大和 VFT 降低，起到抗室性心律失常的作用.

心室机械负荷变化引起的心室电生理变化（收缩兴奋反馈或称机械电反馈）是导致室性心律失常发生的原因之一. 增加左室容量可引起心室 relative refractory period (RRP) 和 effective refractory period (ERP) 缩短、ERP 离散增大，并引发室性心律失常[1,2]. 但心室后负荷增加是否能引起心室电生理参数改变，诱发室性心律失常及抗心律失常药物对其的作用，国内外均未见报道[3,4]. 本文在静注普罗帕酮前后，通过改变在体兔左心室后负荷，观察了心室电生理参数的变化特征及其与室性心律失常发生的关系，以期为心脏负荷改变引起的室性心律失常的抗心律失常治疗，提供理论依据.

MATERIALS AND METHODS

改变在体兔左心室后负荷[5] 大耳白兔 9 只，同济医

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科大学实验动物学部提供，1级，其中♀4只，♂5只，体重2.2±0.3 kg，戊巴比妥钠30 mg·kg^{-1}，iv麻醉，胸骨左缘开胸，保持自主呼吸，维持窦性节律；左侧颈动脉切开、左心室腔内插管，连接TP-400T型压力换能器测定左室内压力．采用自制兔主动脉缩窄夹(缩窄环直径分别为1.5 mm和2.5 mm)，机械性地部分夹闭主动脉根部，分级(A，B级)增加左心室后负荷．另使用PFA-05型输液泵控制性地输注血管扩张剂硝普钠(北京制药工业研究所实验药厂出品，5%葡萄糖500 mL+硝普钠50 mg)，通过降低动脉压，分级(C、D级)减小左心室后负荷．左心室后负荷变化用左心室收缩期压力变化值±ΔP kPa表示．

测定左心室电生理参数 将自制四极心肌插入电极插入左心耳右下缘室间沟左室侧，电极下缘位于左室心尖部．四极电极极间距离：第1－2极，第3－4极均为1.5 mm、第2－3极为10 mm．根据测定的左室电生理参数不同，将第1－2或第3－4极作为刺激电极，相应其余两个电极作为记录电极．连接SEC-3102型刺激器，分别测定a，b两部位的心室舒张阈值(VDT)、相对不应期(RRP)和有效不应期(ERP)或将第2－3极作为刺激电极，相应其余两个电极作为记录电极，连接DF-3A型刺激器，测定室颤阈(VFT)．VDT，RRP、ERP，VFT的测定参照文献[6]．将左心室壁a、b两部位(a，左室前壁；b，左室心尖部)测得的RRP及ERP的最大差值分别定为RRP及ERP离散[7]．VFT的测定在每次测VDT，RRP和ERP后进行，致颤参数：脉宽10 ms，周期30 ms，脉冲发放持续时间1 s．实验通过RM-6000型多导生理仪示波观察并记录资料．Pro(广州明光制药厂出品、每支含3.5 g·L^{-1}、用生理盐水稀释1倍)3 mg·kg^{-1} iv前和用药20 min后[8]、分别在改变左心室后负荷前，部分夹闭主动脉增加左心室后负荷时、除去对主动脉夹闭及输注硝普钠、控制性减小左心室后负荷时、测定左心室电生理参数．

统计学处理 实验结果用配对t检验处理．

RESULTS

逐级增加左心室后负荷(B级，+ΔP=8.4±2.9 kPa)可使左室空间RRP离散和ERP离散分别从11±4和6±3 ms增加到18±8和13±8 ms ($P<0.05$)，VFT从5.5±1.0 V降低到3.9±0.8 V ($P<0.01$)，各实验动物均出现室性心律失常；而逐级减小左室后负荷(C级，−ΔP=2.5±0.8 kPa；D级、−ΔP=5.1±1.1 kPa)、心室电生理各参数无变化($P>0.05$)，各实验动物亦无室性心律失常发生．静注普罗帕酮后，VDT，RRP，ERP，VFT均较用药前显著延长或升高($P<0.01$)；逐级增加或逐级减小左室后负荷，心室电生理参数无显著改变($P>0.05$)，各实验动物均未发生室性心律失常(Tab 1)．

DISCUSSION

在在体动物心脏，Franz等和Dean等[3,4]发现，减小左室后负荷，动作电位时程延长，而增加左室后负荷可使动作电位时程缩短，并出现早期后除极．Reiter亦发现[2]、增加左室容量引起左室ERP缩短，但右室不应期无变化，使左，右心室空间ERP离散增大；另外，左室ERP缩短亦有区域性不均一性．本研究增加左心室后负荷使左室空间RRP离散和ERP离散增加结果与文献报道[2]相一致．导致上述电生理变化的可能机制是：改变左室负荷，改变心室所受到的牵张程度，可导致心肌电缆性质和电容的变化，对心肌牵张程度的改变可导致肌膜对离子通透性改变、但其确切机制还不甚清楚、但可能与牵张依赖性离子通道的存在及特性有关[9]．Todt等发现，Pro能延长心室不应期[10]．且本研究首次发现、对于增加左心室后负荷引起的左室空间RRP和ERP离散增加，亦可通过Pro加以抑制．上述作用可能与Pro阻断通道，延长心室不应期有关[10]．

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Tab 1. Effect of Pro 3 mg·kg^{-1} iv on electrophysiologic changes caused by alteration of left ventricular afterload. $n = 9$ **rabbits,** $\bar{x} \pm s$. **Pre-drug:** $^{a}P > 0.05$, $^{b}P < 0.05$, $^{c}P < 0.01$ *vs* **Pre-changing afterload;** $^{d}P > 0.05$ *vs* **relaxation of clamping aorta; Post-drug:** $^{g}P > 0.05$ *vs* **Pre-changing afterload;** $^{j}P > 0.05$ *vs* **relaxation of clamping aorta;** $^{m}P > 0.05$, $^{o}P < 0.01$ *vs* **Pre-drug. ΔP in LV (Pre-drug): A = 3.5 ± 1.7 kPa; B = 8.4 ± 2.9 kPa; C = −2.5 ± 0.8 kPa; D = −5.1 ± 1.1 kPa. ΔP in LV (Post-drug): A = 3.5 ± 2.5 kPa; B = 6.5 ± 2.3 kPa; C = −2.7 ± 0.7 kPa; D = −4.7 ± 0.9 kPa.**

			Pre-changing afterload in LV	Increasing afterload in LV (clamping aorta)		Release of clamping	Decreasing afterload in LV (nitroprusside iv drip)	
		ΔP in LV	0	A	B	0	C	D
VDT/V	Pre-drug	a	0.8 ± 0.3	0.8 ± 0.3^{a}	1.0 ± 0.3^{a}	0.8 ± 0.2	0.9 ± 0.3^{d}	1.0 ± 0.2^{d}
		b	0.8 ± 0.2	0.8 ± 0.2^{a}	0.8 ± 0.3^{a}	0.8 ± 0.2	0.9 ± 0.2^{d}	0.9 ± 0.3^{d}
	Post-drug	a	1.4 ± 0.6^{o}	1.3 ± 0.4^{go}	1.3 ± 0.4^{go}	1.3 ± 0.3^{o}	1.4 ± 0.3^{jo}	1.4 ± 0.3^{jo}
		b	1.4 ± 0.4^{o}	1.2 ± 0.4^{go}	1.3 ± 0.4^{go}	1.4 ± 0.4^{o}	1.3 ± 0.3^{jo}	1.5 ± 0.3^{jo}
RRP/ms	Pre-drug	a	131 ± 4	134 ± 12^{a}	134 ± 16^{a}	141 ± 17	142 ± 14^{d}	146 ± 13^{d}
		b	131 ± 13	134 ± 17^{a}	140 ± 18^{a}	139 ± 17	141 ± 14^{d}	142 ± 12^{d}
		a − b	11 ± 4	10 ± 9^{a}	18 ± 8^{b}	7 ± 6	0.7 ± 6^{d}	8 ± 6^{d}
	Post-drug	a	173 ± 20^{o}	170 ± 20^{go}	172 ± 16^{go}	178 ± 13^{o}	177 ± 13^{jo}	180 ± 15^{jo}
		b	171 ± 23^{o}	167 ± 17^{go}	176 ± 11^{go}	176 ± 10^{o}	179 ± 15^{jo}	179 ± 14^{jo}
		a − b	9 ± 5^{m}	9 ± 5^{gm}	12 ± 9^{gm}	6 ± 3^{m}	8 ± 4^{jm}	6 ± 4^{jm}
ERP/ms	Pre-drug	a	112 ± 9	117 ± 15^{a}	114 ± 16^{a}	124 ± 16	128 ± 15^{d}	132 ± 17^{d}
		b	115 ± 13	118 ± 16^{a}	121 ± 21^{a}	123 ± 13	130 ± 18^{d}	132 ± 18^{d}
		a − b	6 ± 3	4 ± 3^{a}	13 ± 8^{b}	4 ± 3	3 ± 2^{d}	3 ± 2^{d}
	Post-drug	a	156 ± 19^{o}	155 ± 19^{go}	151 ± 19^{go}	162 ± 16^{o}	162 ± 18^{jo}	163 ± 18^{jo}
		b	153 ± 25^{o}	156 ± 16^{go}	158 ± 14^{go}	160 ± 16^{o}	162 ± 16^{jo}	162 ± 18^{jo}
		a − b	8 ± 7^{m}	7 ± 6^{gm}	13 ± 11^{gm}	6 ± 0.3^{m}	5 ± 4^{jm}	7 ± 4^{jm}
VFT/V	Pre-drug		5.5 ± 1.0	5.1 ± 0.6^{a}	3.9 ± 0.8^{b}	5.6 ± 1.0	5.5 ± 0.9^{d}	5.2 ± 1.0^{d}
	Post-drug		9.3 ± 1.8^{o}	8.4 ± 1.8^{go}	7.2 ± 1.6^{go}	9.3 ± 1.6^{o}	9.2 ± 1.8^{jo}	9.2 ± 1.6^{jo}

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