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Evaluation of QAI as an index of cardiac contractility in conscious telemetered rats

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The assessment of compound effects on cardiac contractility is an important part of cardiovascular safety pharmacology studies. However, the requirement for complex invasive surgery or tethering has meant that, methodologies describing contractility measurements in the conscious rat have been limited. This study describes the validation of the QA interval (QAI) as an indirect index of cardiac contractility in conscious telemetered rats. QAI is the time interval from the Q point on the ECG to point A, initiation of the upstroke in the aortic pressure wave, and is inversely proportional to cardiac contractility (Cambridge *et al.,* 1986). By using diverse inotropic agents, we assessed the relationship between QAI and contractility. QAI was measured in male Sprague-Dawley rats (n=5; 400-700g) implanted with DSI C50-PXT rat telemetry transmitters to measure arterial blood pressure and ECG. Animals were then dosed with positive (salmeterol; 0.003. 0.01 and 0.03 mg/kg and milrinone; 0.3, 3.5 and 10.5 mg/kg) and negative (verapamil; 3, 10 and 30 mg/kg) inotropic drugs and data was recorded for 24 hours. Left ventricular contractility (LVdP/dt_{max}) was directly measured in a separate group of conscious animals (n=4, 400-550g) implanted with DSI mouse PA-C10 transmitters with the pressure catheters inserted into the left ventricle via the apex of the heart. Each rat was administered with the highest dose used in the QAI assessment and data was recorded for 24 hours. Salmeterol and milrinone produced statistically significant (analysis of variance, $p<0.05$) and dose dependent decreases in QAI and increases in LVdP/dt_{max}. Verapamil produced a statistically significant increase in QAI and a decrease in LVdP/dt_{max} (Table 1). Further analysis of our results revealed a log-linear relationship for QAI and LVdP/dt_{max} correlations.

Table 1: Peak effects of highest dose (HD) administration on QAI and LVdP/dt_{max} (mean values ± s.e.m).

	QAI (ms)		LVdP/dt_{max} (mmHg/ms)	
Compound	Vehicle	HD	Vehicle	HD
Salmeterol	51.93 ± 0.50	48.56 ± 0.54		9612 ± 375
Milrinone	50.41 ± 0.43	47.55 ± 0.43	7670 ± 252*	10003 ± 439
Verapamil	50.60 ± 0.46	55.46 ± 0.46		5552 ± 164

* *single vehicle (purified water) used for LVdP/dt_{max} studies*

Although only limited evaluation of this model has been demonstrated in this study, we propose that QAI can be used as an indirect predictor of cardiac contractility in the telemetered rat. These findings indicate that it may be possible to use less surgically invasive models to assess the effect of novel compounds on cardiac contractility, enabling early cardiovascular de-risking of drugs, at reduced cost

Cambridge D *et al.* (1986) *Cardiovas. Res.* 20(6):444-50