Continuous Cardiac Output Monitoring in Conscious Sprague-Dawley Rats

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Background & Objective

Traditionally cardiac output (CO) measurements required either anesthesia or physical tethering to an external system. This results in limitations to duration of monitoring (acute effects only or longitudinal snapshot) and/or throughput (1:1, animal to hardware). EndoGear4 (EG4, Transonic Systems Inc., Ithaca, NY) is an implantable telemetry system that allows continuous aortic blood flow (used to calculate cardiac output) in conscious, freely moving rats.

The objective of this study was to use amlodipine and carvedilol to assess the ability of the EG4 system to continuously monitor changes in cardiac output in a conscious rat, over the course of 24 hrs.

Materials & Methods

All procedures in this study were conducted on an approved IACUC protocol and are in compliance with the Guide for the Care and Use of Laboratory Animals.

Telemetry Surgery:
Adult, male CD rats were implanted with the EndoGear4 (EG4) device, under isoflurane anesthesia (1.5-3%). The flow probe (2.5PSB) was placed around the ascending aorta using a right lateral thoracotomy approach and the pressure catheter was inserted into the iliac aorta. The implant body was placed intraperitoneally. The power inductance unit was placed in a subcutaneous pocket and secured using surgical mesh. All animals were recovered for a minimum of 6 days, with optimized post-surgical care, prior to dosing.

Hardware/Software:
Data from EG4 implants was acquired wirelessly (300Hz) using a PowerLab 16/35 and LabChart Pro (v8) software (ADInstruments, Colorado Springs, CO). Data was analyzed using LabChart Pro (v8).

Telemetry Study:
The study was executed in multiple phases, using a Latin square crossover design, with a minimum of 4 days between each dose and 6 days between each phase.

Table 1: Study Design

Treatment	Dose Level (mg/kg or mpk)	Dose Conc (mg/mL)	Dose Volume (mL/kg)	n
Control*	0	0	5	9
Amlodipine - LOW	10	2		
Amlodipine - HIGH	30	6		
Carvedilol - LOW	100	20		
Carvedilol - HIGH	300	60		

* 0.5% methylcellulose, reverse osmosis water

Table 2: Phase A

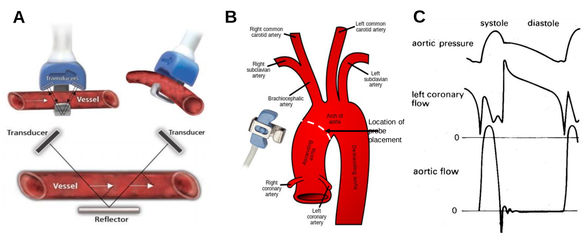
Dose 1	Dose 2	Dose 3	Animal ID
Control	Carvedilol - LOW	Amlodipine - HIGH	1001, 1002, 1003
Amlodipine - HIGH	Control	Carvedilol - LOW	1004, 1005, 1006
Carvedilol - LOW	Amlodipine - HIGH	Control	1007, 1008, 1009

Table 3: Phase B

Dose 4	Dose 5	Dose 6	Animal ID
Control	Carvedilol - HIGH	Amlodipine - LOW	1001, 1002, 1003
Amlodipine - LOW	Control	Carvedilol - HIGH	1004, 1005, 1006
Carvedilol - HIGH	Amlodipine - LOW	Control	1007, 1008, 1009

Statistics:
All data are shown in raw numerical form. Data in telemetry plots are mean ± standard error of the mean (SEM). For simplicity, data in Table 1 were derived from mean values (2 to 4 hours post dose administration) and summarized as absolute differences (double-delta, baseline (BL) and control-corrected).

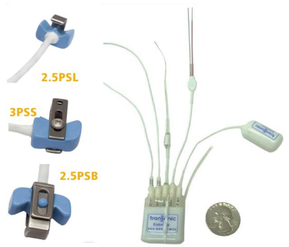
Figure 1: Aortic Flow Measurement 101



A: Schematic of transit-time flow probe placement around vessel. The advantage of this (over Doppler flow) is vector independence and velocity integration over the entire cross section of the vessel. B: For cardiovascular studies, the flow probe is placed around the ascending aorta. C: Corresponding hemodyamic waveforms, relative to the cardiac cycle.

Figure 2: EG4 Telemetry Implant

Standard EG4 implant, with varying flow probe styles.



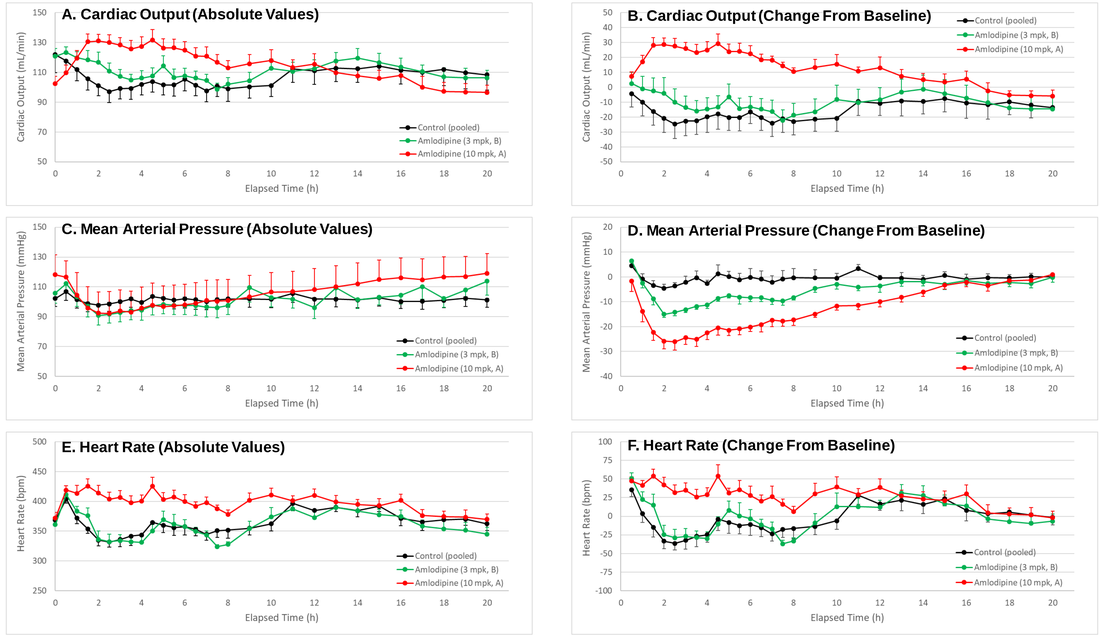
Hardware:
Flow: configurable channels
- Pre-calibrated
- Different styles (lateral, side, back)
- Usage sites: aorta, carotid, renal artery

Biometrics: 1 or 2 channels
- Pressure
- ECG

Temperature: up to 2 channels
Power:
- Inductance technology eliminates need for battery life considerations

Figure 3. Amlodipine Increases Cardiac Output

Angioselective Ca-channel antagonist: baroreflex-mediated chronotropy/inotropy



Notes: Phase A, n=9; Phase B, n=7-9; control data pooled from Phases A & B

Figure 4. Carvedilol Decreases HR/MAP

B1/β2-, α1-adrenergic receptor antagonist

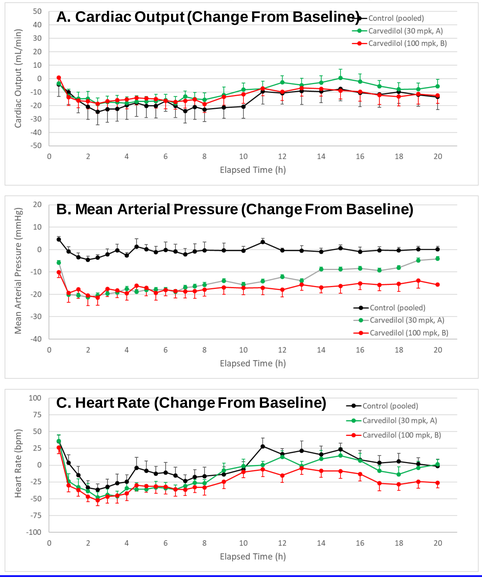


Table 4: Peak Hemodynamic Effects, Summary

BL, Control-corrected	Amlodipine		Carvedilol	
	3 mpk	10 mpk	30 mpk	100 mpk
Heart Rate (bpm)	+3	+54	-12	-16
Mean Arterial Pressure (mmHg)	-10	-22	-17	-17
Cardiac Output (mL/min)	+10	+48	+5	+5

Conclusions

1. Continuous cardiac output measurements can be acquired reliably from a rodent preclinical model (up to 9 weeks post surgery)
2. Administration of 10 mpk amlodipine resulted in increased cardiac output mediated by baroreflex sympathetic activation; 3 mpk showed dose-dependent effects on MAP, but not CO/HR
3. Administration of carvedilol demonstrated a clear vasodilatory effect, but muted impact on HR and CO.

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