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Original article

Translational assessment of cardiac contractility by echocardiography in the telemetered rat

Hai-Ming Tang [a,*], Haisong Ju [a], Shufang Zhao [b], Carrie LaDuke [a], Suzette Hahn [a], James Glick [c], Cynthia Carey [a], Gregory S. Friedrichs [a]

[a] Safety Pharmacology, Preclinical Safety, Novartis Institute for Biomedical Research, East Hanover, NJ, United States
[b] Translational Imaging, BioMarker Development, Translational Medicine, Novartis Institute for Biomedical Research, East Hanover, NJ, United States,
[c] DMPK, Early Bioanalytics and Technology, Novartis Institutes for Biomedical Research, East Hanover, NJ, United States

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ABSTRACT

Introduction: Cardiac contractility was evaluated using standard inotropic agents in rats. We compared indices of cardiac contractility, i.e. LV dP/dt max from telemetry while simultaneously collecting EF (ejection fraction) and FS (fractional shortening) measures from echocardiography.
Methods: Male Wistar rats were instrumented with telemetry devices for measurements of blood pressure and left ventricular pressure. Milrinone (PDE III inhibitor) and verapamil (L-type calcium channel blocker) at doses of 0, 3, 10, and 30 mg/kg were administered orally using a 4 × 4 Latin square crossover study design. Telemetry data were recorded at predose and continuously for 24 h post-dose. Echocardiographic evaluations were conducted once at predose and at 1 and 2 h after milrinone or verapamil administration, respectively. During the recording of echocardiograms, telemetry data were collected simultaneously. Blood samples were also collected to confirm plasma drug exposure.
Results: As expected, milrinone increased LV dP/dt max, EF and FS while verapamil decreased LV dP/dt max, EF and FS. Linear regression analysis showed a positive correlation between LV dP/dt max and EF or FS ($P < 0.001$) with both test agents. A change in LV dP/dt max of 1000 mmHg/s was found to correspond with a change in EF and FS of 13 and 16%, respectively, in the telemetered rat.
Discussion: The correlation between contractility indices assessed by telemetry and echocardiographic methods in rat models has not received much attention to date. Our results with two reference compounds demonstrate that both methods are sensitive to alterations in contractility induced by inotropic agents administered to rats. The high degree of correlation between changes in LV dP/dt max and EF or FS in the rat enables a translational-element of clinical relevance following changes in contractility indices when measured with telemetry devices in preclinical studies.

1. Introduction

Cardiac contractility evaluation in preclinical animal models has gained more attention in recent years within the field of safety pharmacology. Cardiac contractility indices such as LV dP/dt max are measured commonly in preclinical studies using conscious telemetered animals (Stehlin et al., 2013; Carroll, Zenebe, & Strange, 2006; McKee, Daller, Baumgartner, & Pettinger, 2014; Adeyemi et al., 2009; Sato, Kandori, & Sato, 1994). However, LV dP/dt max measurements in the clinic are impractical due to its invasive nature, where noninvasive methods such as echocardiography are routinely used to assess cardiac function in patients (Hanton, Eder, Rochefort, Bonnet, & Hyvelin, 2008; Pombo, Troy, & Russel, 1971; Jones, Ewy, & Groves, 1975; Kraunz & Ryan, 1971). The translation of preclinical contractility indices to clinical meaning or functional consequence has not been described. A recent HESI initiative aims to narrow this gap by investigating the effects of several reference compounds on cardiac contractility in dogs using both telemetry and echocardiographic methods (Guth et al., 2015, personal communication). Cools et al. (Cools et al., 2014) describes a linear relationship between dP/dt max and ejection fraction (EF) in conscious dogs approximating 1000 mmHg/s change in dP/dt max is equivalent to a 7% change in EF. Similar translational assessment in anesthetized dogs by Derakhchan et al. was presented at the 2014 Safety Pharmacology Society conference (Derakhchan, Sutherland, Chui, & Vargas, 2014). While such translational assessments provided valuable information in dogs, similar assessment has not been conducted in rats or other

* Corresponding author.
E-mail address: hai-ming.tang@novartis.com (H.-M. Tang).

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species. The rat is routinely used in drug safety assessment and is known to have good predictive value for hemodynamics changes (Aguirre, Heyen, Collette, Bobrowski, & Blasi, 2010; Blasi et al., 2012). In this study, we utilized positive (milrinone, a phosphodiesterase III inhibitor) and negative (verapamil, a calcium channel blocker) inotropes to investigate a potential translational relationship of contractility indices in the rat.

2. Materials and methods

2.1. Animals

This study was conducted in accordance with the Novartis Animal Care and Use Committee-approved protocol in compliance with the guidelines provided by the Guide 8th edition and with facility Standard Operating Procedures (SOPs).

Male Wistar Han rats were obtained from Charles River Laboratories, Portage, MI. At the initiation of dosing, they were approximately 17 weeks of age and weighed 358 to 412 g. Rats were single-housed in solid bottom cages and provided Certified Rodent Diet 18% #5LG3 pellets (PMI Feeds, Richmond, Indiana), ad libitum. Water was provided ad libitum from water bottles. Environmental enrichment was provided to animals (e.g., nylon bones/balls, BioServ® certified rodent crumbles ™, and/or mouse bio-huts). Water was periodically analyzed for microbial and chemical contaminants. Environmental controls for the animal room were set to maintain 68 to 76°F, a relative humidity of 30 to 70%, and a 12-h light/12-h dark cycle.

2.2. Telemetry

Six male rats were each implanted with a telemetry transmitter (TRM54PP, Millar Inc., Auckland, New Zealand) for measurements of arterial blood pressure, left ventricular pressure (LVP), and body temperature. Surgeries were performed using aseptic techniques under general anesthesia. The animals were anesthetized with isoflurane and mechanically ventilated. A midline laparotomy was made and the diaphragm incised to expose the pericardium and the heart. A purse string suture was loosely placed at the apex of the heart. Through the middle of the purse string suture a needle was used to puncture the apex of the heart into the left ventricle. The pressure catheter was inserted into the ventricle and secured with the previously placed purse string suture for measuring left ventricular pressure. The diaphragm was closed with an absorbable suture. A second pressure catheter was inserted into the abdominal aorta just below the renal arteries for measuring systemic blood pressure. The telemetry device body was placed within the abdominal cavity and attached to the muscle of the abdominal wall using a mesh pouch and non-absorbable suture. The peritoneum and abdominal muscle were closed with an absorbable suture. The animals were allowed to fully recover at a minimum of 2–3 weeks prior to study initiation.

2.3. Echocardiography

Echocardiography was performed in animals lightly anesthetized with isoflurane (3% induction and 1–2% maintenance) delivered in

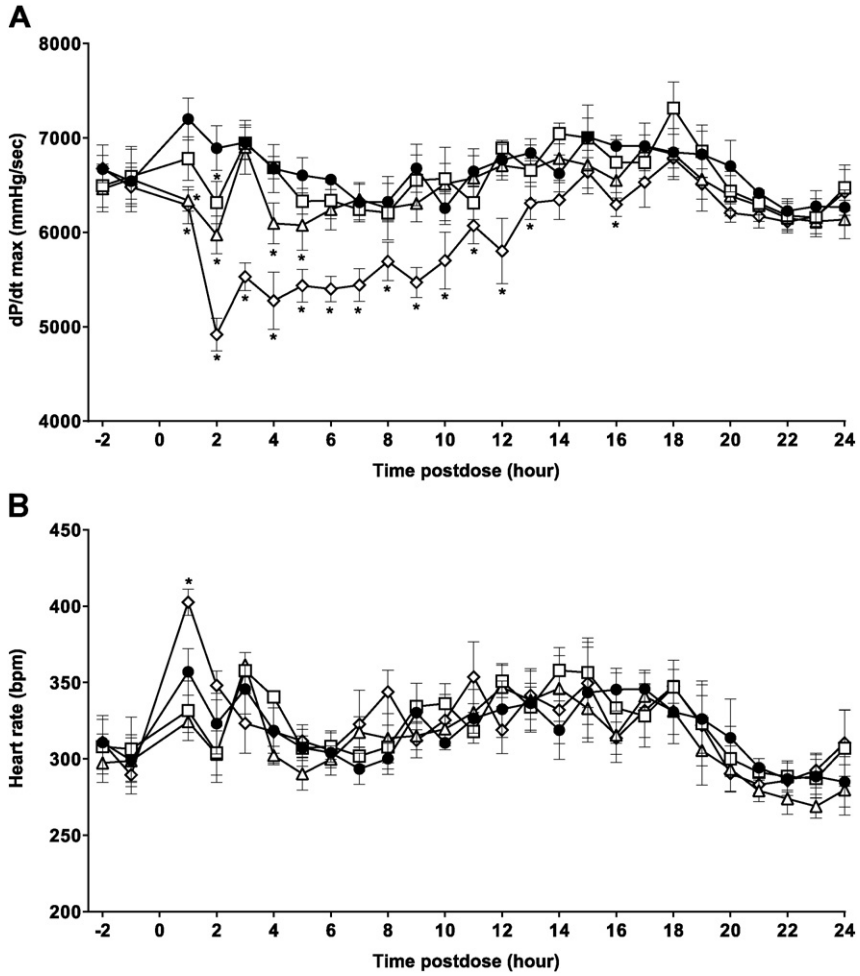

Fig. 1. Cardiovascular effects of verapamil in conscious rats. (A) dP/dt max. (B) Heart rate. Vehicle (●), 3 (□), 10 (△), and 30 (◇) mg/kg po (n = 4). Telemetry data were continuously recorded for 2 h predose and 24 h post-dose. Data shown are the average of 1 h periods. bpm: beats/min. Error bars represent standard error (SEM). *P < 0.05 when compared to the vehicle.