Webinar: The Assessment of Cardiac Function in Nonclinical Safety Studies

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- One hour presentation; reserving 30 minutes for Q&A (submit questions anytime using the Q&A, expand to view)
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Assessment of Cardiac Function in Nonclinical Safety Studies

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Fundamental Properties of the Heart

- **Inotropic**
  - Effect on the “strength of contraction” of cardiac muscle
  - *Inotropy* and *contractility* are often used interchangeably
  - The focus of this webinar

- **Chronotropic**
  - Effect on Heart Rate

- **Dromotropic**
  - Effect on conduction velocity (primarily AV node)

- **Lusitropic**
  - Effect on myocardial relaxation

- **Bathmotropic**
  - Effect on excitability or irritability of heart muscle
Cardiac Contractility

- Cardiac contractility is defined by physiologists as the intrinsic ability of cardiac muscle to do work at constant end-diastolic fiber length (Katz 1977).

- Thus, with increased contractility, the heart performs more work at the same diastolic fiber length (end-diastolic volume).
Contractility vs Inotropic State

- The terms are often used interchangeably
- A positive inotropic drug (positive inotrope) causes an increase in contractility
- A negative inotropic drug (negative inotrope) causes a decrease in contractility
Consequences of Changing Contractility

- Decreased contractility is clinically important since it results in a reduction in the heart’s ability to perform work
  - Significant reduction in cardiac contractility manifests clinically as acute or chronic heart failure
  - *If you were developing a drug for chronic use in elderly, diabetic, obese, hypertensive, heart failure patients, wouldn’t you want to know about this?*

- Increased contractility increases the work performed by the heart and is a normal physiological response to increased demand
  - However, it dramatically increases myocardial oxygen consumption
  - *If you were developing a drug for patients with decreased coronary reserve due to coronary stenosis and myocardial ischemia, wouldn’t you want to know about this?*
Aortic valve closes
A-V valve opens
A-V valve closes
Electrocardiogram
P wave
Q wave
R wave
S wave
Although the general concept of contractility is often understood, its actual measurement is fraught with problems!

Assumptions and limitations of a contractility index must be understood or misinterpretations are likely.
Contractility Indices

- In addition to being affected by actual changes in intrinsic contractility, all indices commonly used in preclinical and clinical studies are affected by changes in preload, afterload and heart rate as well.

- Thus, a drug-induced change in any of these parameters can indirectly affect an index of contractility without actually changing the intrinsic contractile function of the myocardium itself.
How Can Contractility Be Measured?

- **Muscle twitch velocity**
  - Hill experiments in frog Sartorius muscle (pioneering studies)

- **Ejection Fraction (stroke volume ÷ end-diastolic volume)**
  - Extremely afterload dependent
  - Often measured with echocardiography or impedance catheters

- **dP/dt_{max}** (an in vivo approximation of muscle twitch velocity)
  - Preload and HR dependent
  - Slightly less afterload dependent since it occurs prior to aortic valve opening

- **Time varying elastance model (ESPVR, E_{max})**
  - PV Loops
  - The Gold Standard

- **QA interval** – an approximation of the average rate of isovolumic systolic pressure development
Frank-Starling Mechanism
“Starling Law Of The Heart”

Cardiac function changes with preload
Curves are displaced with changes in contractility
The End Systolic Pressure Volume Relationship (ESPVR)

$E_{\text{max}} = \text{Slope of ESPVR}$

Also known as the “Time Varying Elastance Model

Suga, H., Sagawa, K., Shoukas, A.
Circ. Res. 1973

The only preload and afterload independent measure of inotropy!
dP/dt (first derivative of LVP)

- **dP/dt** is the instantaneous slope of the LVP curve.
- **dP/dt_{max**} is the maximum value of that slope during a cardiac cycle.
- \( A = dP/dt_{40}, \) early isovolumic systole
- \( B = dP/dt_{max} \)
- \( C = dP/dt, \) late isovolumic systole
Normal & Heart Failure

Note: Decreased Systolic Pressure (AoP and LVP)
Decreased $dP/dt_{\text{max}}$
Increased LVEDP
Increased HR
The QA Interval

Indirect measure of the duration of isovolumic systole without LVP measurement.

Also includes the time for depolarization, conduction, excitation-contraction coupling and time required for propagation of the pressure wave to the arterial pressure sensor.

All are assumed to be constant.
QA Interval Assumptions

- Average dP/dt (ΔP/Δt) varies linearly with dP/dt_max
- Developed pressure is constant (preload and afterload)
- Na⁺ channels are unaffected
- Excitation-contraction coupling is unaffected
- Wave propagation velocity between the heart and the arterial pressure sensor is unaffected
  - No change in compliance of the conductance vessels

"Thus, QA depends on many factors other than myocardial contractility” R.H. Hamlin
Nonetheless, QA Can Work Empirically With Pure Inotropic Drugs

- References:
  - Cambridge, 1986
  - Adeyemi, 2009
  - Norton, 2009

- Can provide an inexpensive screen for drug effects on contractility in discovery or lead optimization

- Usage as a definitive indicator of cardiovascular safety in IND-enabling studies is questionable
Contractility Indices - Summary

- All but ESPVR are sensitive to preload and afterload changes.
- If preload, afterload, and HR are constant in treated and control groups, \(\frac{dP}{dt_{\text{max}}}\) provides a robust and sensitive index of the inotropic effects of drugs in experimental animals.
- These three parameters must be measured and \(\frac{dP}{dt_{\text{max}}}\) data must be interpreted with them in mind.
• Overview on the heart and morphology of the signals
• Force-frequency relationship
• Validation compounds
• Case studies
Inotropy (LVdP/dtmax)
Force-frequency relationship
(positive Bowditch staircase)
Lusitropy (LVdP/dtmin)
Effect of pos. inotropic compound on LVP

LVdP/dt_{40}

Relatively insensitive of pre-load
Effect of positive inotropic compound on Bowditch staircase
Effect of a compound with slight increase in heart rate and increase in contractility
No effect on heart rate
Pos lusitropy
β3 Agonist
Verapamil
Ca++ antagonists impair relaxation

Verapamil
Typical pos. inotropic effect,

$\uparrow \text{LVdP/dtmax}$ $\downarrow \text{LVEDP}$
Case studies
Telemetry dog n = 4

Median of 10 min
Compound X2

Telemetry dog n = 4

- 0 mg/kg
- 1 mg/kg
- 3 mg/kg
- 10 mg/kg

Median of 10 min
Summary

- Contractility is an important, intrinsic characteristic of cardiac function.
- Controlled physiologically by autonomic input to match cardiac output to metabolic demands.
- Is markedly influenced by drugs, including adrenergic agents, calcium antagonists, etc.
- May be modulated both positively and negatively by drugs of all kinds (off target effects).
Cardiac contractility in safety pharmacology

- Variety of indices allow for the assessment of drug-induced effects on cardiac contractility
  - e.g. LV dP/dtmax can be integrated into safety pharmacological studies
- A sensitive index to changes in contractility but also influenced by HR, EDLVP
- Contractility assessment can add to overall safety evaluation of new pharmaceuticals
Questions

● Does introduction of an LV pressure transducer lead to arrhythmias?
● In what species can LVP be measured?
● What magnitude of changes in e.g. LVdP/dt can be of relevance? What magnitude of change can be detected with such models?
Backup
Drug-induced changes in contractility

- Positive inotropic stimulation
  - Increased incidence of proarrhythmia (VT/VF, atrial fibrillation)
  - Increased mortality (catecholamines, PDE-III-inhibitors)

- Negative inotropic effects
  - Increased mortality in patients with acute/chronic heart failure (e.g. calcium antagonists like verapamil)

Haverkamp, 2009