Suggested papers on hemodynamic assessments

Matt Skinner, PhD, DSP
• Importance of drug-induced effects on the CV system

• Effects of test articles on mechanical/hemodynamic effects may have more impact on human morbidity/mortality then Ephys effects.

• Which mechanical/hemodynamic properties to focus on?

• Paper catalogues cardiovascular parameters that, if affected, may translate to increased mortality and morbidity.
• General description of cardiovascular system

• Important equation:

\[ \text{PAo} = \text{CO} \times \text{svr} \]
The catalogue of parameters

- **Heart rate**
  - faster HR, more oxygen consumption, shorter diastole when coronary flow occurs

- **Inotropic state** (contractility)–
  - definition of inotropy
  - limitations of $dP/dt_{\text{max}}$ (contractility is only 1 of a number of determinants of this)
  - QA interval (contractility is only 1 of a number of determinants of this)

- **Lusitropic state** (ease of filling)
  - $dP/dt_{\text{min}}$, tau, ventricular filling

- **Hindrance** (afterload, impedance, resistance)

- **Venous system**

**General description of PV loops**

Hamlin and del Rio, 2012
Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers

Daniel Burkhoff,1 Israel Mirsky,2 and Hiroyuki Suga3
1Division of Cardiology, Department of Medicine, Columbia University, New York, New York; 2Divisions of Mathematical Biology and Cardiology, Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts; and 3Research Institute, National Cardiovascular Center, Suita, Osaka, Japan

• General overview of PV loops – the gold standard for contractility assessment

• Basic concepts sections
  • Systolic properties
  • Diastolic properties
• Very useful paper detailing approaches used to explore and understand vascular drug action in vivo. Useful for follow-up cardiovascular studies.

• Change in hemodynamic parameters in regulatory SP CV studies often only give general description of drug effect – no mechanistic info

• When we apply drug to fully integrated system we often measure an amalgamation of responses: direct, reflex, local effects.
Techniques described to tease these effects apart; need to perturb the system:

- use of ganglion blockers
- pharmacological blockade of autonomic effectors eg Ach, noradrenaline, angiotensin II, vasopressin, baroreceptor block, local autocoid block, e.g. NO, prostacyclin, thromboxane A2, endothelin

Block eliminates the reflex adjustments that occur in intact animal when BP changes. Instead we can see the direct effect on cardiac and vascular tone.

Difficult to assess effects on vasculature after oral or i.v. dose if compound also has effect on heart.

- benefits of intra-arterial infusion
- examine local effects on a vascular bed without confounding systemic effect
- rule of thumb - 1/10th of i.v. dose

Wright and Angus, 2000
Assessing baroreceptor reflex:

- Need fully intact system to assess effect on autonomic reflex.
- Generate a heart rate MAP curve by:
  - Sodium nitroprusside to decrease MAP and cause tachycardia
  - Phenylephrine to increase MAP and cause bradycardia

Section on assessing potential for causing postural hypotension

Wright and Angus, 2000
Echocardiography, a non-invasive method for the assessment of cardiac function and morphology in preclinical drug toxicology and safety pharmacology

Gilles Hanton1, Véronique Eder, Gael Rochefort, Pierre Bonnet & Jean-Marc Hyvelin

1Pfizer Global Research and Development, Department of Toxicology and Comparative Medicine, Z.L. Puteaux, BP 159, F-77401 Ambilly Cedex, France

- Review paper giving general introduction to echocardiography
- Reviews main modes used:
  - 2D echo (short and long axis)
  - M-mode echo
  - Doppler echo
- Section on use in tox and safety pharm studies

Figure 2. Example of a 2-D longitudinal section of the heart in a dog by 2-D echocardiography.

Figure 7. Transventricular M-mode echocardiography in a dog. The guidance line has been placed at the level of the tip of the mitral valves in a longitudinal section (Figure 2) or between the chordae tendinae in a transverse section (Section C on Figure 3). The M-mode recording shows the changes over time in the right ventricle cavity, the interventricular septum, the left ventricle cavity and posterior wall of the left ventricle.
RESEARCH PAPER

Sunitinib, a Receptor Tyrosine Kinase Inhibitor, Increases Blood Pressure in Rats without Associated Changes in Cardiac Structure and Function

E. Blasi,1 J. Heyen,1 S. Patyna,2 M. Hemkens,1 D. Ramirez,1 A. John-Baptiste,3 J. Steidi-Nichols4 & A. McHarg1

1 Safety Pharmacology-Pfizer Global Research and Development, La Jolla, CA, USA
2 Clinical Development-Pfizer Global Research and Development, La Jolla, CA, USA
3 Drug Safety Biomechanics-Pfizer Global Research and Development, La Jolla, CA, USA
4 Safety Pharmacology-Pfizer Global Research and Development, Groton, CT, USA

Pfizer

The contribution of VEGF signalling to fostamatinib-induced blood pressure elevation

M. Skinner,1 K. Philip,1 D. Lengel,1 L. Coverley,1 E. Lamm Bergström,1 P. Glaves,1 H. Manghreve,1 H. Prior,1 M. Braddock,1 R. Huby,1 J. O. Curvers1, P. Duffy1 and A. R. Harmer1

1AstraZeneca R&D, Macclesfield, UK
2AstraZeneca R&D, Whatham, MA, USA, and
3AstraZeneca R&D, Mölndal, Sweden

AstraZeneca

RESEARCH PAPER

Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone

M. Forrest,1 D. Bloomfield,1 R. Briscoe,1 P. N. Brown,1 A. M. Cumiskey,1 J. Ehrhart,2 J. C. Hershey,3 W. J. Keller,2 X. Ma,1 H. E. McPherson,2 E. Messina,1 N. S. Peterson,1 W. Shinar-Rodriguez1, P. K. Siegl2, F. J. Sinclair2, C. J. Sparrow3, A. S. Stevenson1, S. Y. Sun1, C. Tsai1, H. Vargas,2,6, M. Walker3,4, S. West,3,4, V. White4 and R. F. Woltmann2

Merck

Real life CV hemodynamic investigations

Boehringer Ingelheim
Real life CV hemodynamic investigations

All 4 studies used a variety of hemodynamic assessments either for follow-up problem solving or during LO for compound selection

- Rodent telemetry (4)
- Anaesthetised rat (4)
  - Adrenalectomy
  - Endothelial function
  - Echocardiography
  - Pithing
  - Perfused hindlimb
- Dog/monkey telemetry (2)
- Anaesthetised dog (2)
- Isolated heart and vessel (2)

All good ‘real life’ examples of CV SP in action using many of the techniques described in the previous papers
References

An approach to the assessment of drug-induced changes in non-electrophysiological properties of cardiovascular function.
Hamlin RL, Del Rio C.

Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers.
Burkhoff D, Mirsky I, Suga H.

Techniques to measure pharmacodynamics in the intact vasculature.
Wright CE, Angus JA.

Echocardiography, a non-invasive method for the assessment of cardiac function and morphology in preclinical drug toxicology and safety pharmacology.
Hanton G, Eder V, Rochefort G, Bonnet P, Hyvelin JM.

Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone.

Sunitinib, a receptor tyrosine kinase inhibitor, increases blood pressure in rats without associated changes in cardiac structure and function.

Strategic integration of in vivo cardiovascular models during lead optimization: predictive value of 4 models independent of species, route of administration, and influence of anesthesia.
Fryer RM, Harrison PC, Muthukumarana A, Nodop Mazurek SG, Ng KJ, Chen RR, Harrington KE, Dinallo RM, Chi L, Reinhart GA.

The contribution of VEGF signalling to fostamatinib-induced blood pressure elevation.