

Scisense PV Technical Note

Cardiac Hemodynamic Assessment using Pressure Volume (PV) Loops in Safety Pharmacology

Safety Pharmacology continues to be a rapidly developing discipline in a regulatory-driven process to generate data to inform risk/benefit assessment. In the cardiac field of study the aim of Safety Pharmacology (SP) is to characterize the pharmacodynamic/pharmacokinetic (PK/PD) relationship of a drug's adverse effects in the heart and circulation. Unlike toxicology, safety pharmacology includes a regulatory requirement to predict the risk of rare lethal events such as torsades de pointes (TdP) syndrome.

IMPORTANCE OF CARDIAC HEMODYNAMIC ASSESSMENT IN DRUG DISCOVERY AND EVALUATION

As an example of the importance of testing for potential adverse cardiovascular effects, in the mid 1990's the antihistamine, terfenadine (Seldane), was withdrawn following a growing awareness that the drug could evoke the potentially life threatening cardiac syndrome, torsades de pointes (TdP) or polymorphic ventricular tachycardia, in otherwise healthy patients (1). TdP reaction from this antihistamine only became evident after several millions of prescriptions, put many people at risk. This incident, and others like it in the late 1980s and early 1990s, gave rise to specialization of safety pharmacology, which was not previously recognized as very relevant. From this came safety testing for cardiovascular impact of non-cardiovascular drugs consisting of the evaluation of QT interval prolongation to screen for TdP liability.

Recent SP approaches using ECG measurements include measurements of QT interval as a surrogate biomarker of cardiac biopotentials (1, 2, 9). For example, non-cardiovascular indicated drugs such as droperidol, lidoflazine, and cisapride were removed from market solely based on the QT interval. Clinicians are constantly faced with both older and newly approved drugs labelled as potentials for TdP. While at the same time drugs considered to be safe in non-clinical studies may be found to have QT-liability (proarrhythmic risk) in early clinical studies (2). Regulatory authorities might ask for scientific rationalization for this incongruity and, as long as the safety of subjects in later phase clinical trials is assured, the sponsor may then decide whether to continue or terminate the drug development in light of the risks.

SAFETY PHARMACOLOGY GUIDELINES

The S7A: Safety Pharmacology Studies for Human Pharmaceuticals guideline for the conduct of safety pharmacology evaluations recommends using a core battery of studies on three vital organ systems (cardiovascular, respiratory and central nervous system) to assess the potential risks of novel pharmaceuticals for human use.

Core Cardiovascular Studies:

- Central arterial pressure
- Heart rate
- Electrocardiogram (ECG)
- Electrophysiology (hERG)

Supplemental Cardiovascular Studies:

- Cardiac output
- Ventricular contractility
- Ventricular resistance

Cardiac Hemodynamic Assessment in Safety Pharmacology Cont.

TRADITIONAL METHODS OF ASSESSMENT IN PRE-CLINICAL SAFETY PHARMACOLOGY

Cardiac and hemodynamic studies have the potential for significant variation between investigators as the ability to detect adverse effects is subjective and sometimes inconsistent. For detecting adverse effects of tested (candidate) drug on cardiac contractility, pre-clinical safety pharmacology mostly uses a combination of ECG with a pressure catheter to study QA interval compared with LV dP/dt max (Fig. 1). This set up allows for a two-index comparison of heart contractility to assess the inotropic induction (3, 4, 5). The QA interval covers the period of time of initial depolarization of ventricles (R decline) until the time when the aortic valve opens. For the purpose of determining the QA interval, the time between the Q on the ECG and the beginning of the upstroke on the arterial blood pressure is used as an indicator of altered LV contractility (Fig. 1). Drugs that slow conduction velocity through the heart could prolong the QA, and may have more effect on QA than on LV dP/dt max. Theoretically, reduction of blood pressure induced by the candidate drug causing reduced arterial stiffness might reduce pulse wave propagation and thus QA interval. Moreover, QA captures reduced contractility more precisely than compared to increased contractility.

Other safety pharmacologists use the LV dP/dt max-HR relationship to determine the force-frequency relationship while singling out LV dP/dt max as a measure of pharmacodynamic heart contractility endpoint (6). It is important to note that many drugs induce both chronotropic and inotropic effects which changes HR along with LV dP/dt max and that LV dP/dt max changes with HR. Thus changes to contractility must be evaluated based on the corresponding changes in heart rate (6).

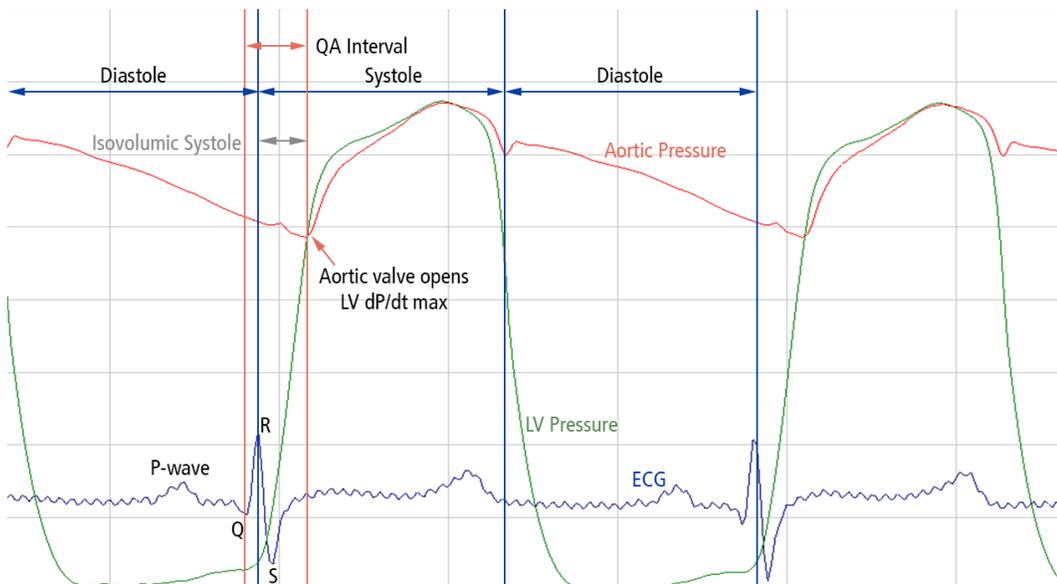


Fig. 1: QA interval approximates of the average rate of isovolumic systolic pressure development.

PV LOOPS IN PRE-CLINICAL SAFETY PHARMACOLOGY

Recently, Conductance and Admittance PV loop technology has been used for screening and pharmacologic assessment of the inotropic state of the heart (7, 8). While this method is the gold standard for investigation of cardiac function with respect to clinical disease, it is currently not widely used in safety pharmacology (7). By using the relationship of pressure and volume for interrogation of the LV, safety pharmacologists can better determine lusitropic effects of myocardial relaxation that cannot be otherwise captured by using two indices comparison (e.g. QA interval with LV dP/dt max). Moreover, other important parameters of load independent measurements such as ESPVR, EDPVR, PRSW, PVA can be determined, strengthening conclusions about the tested drug candidate.

Cardiac Hemodynamic Assessment in Safety Pharmacology Cont.

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