Respiratory Safety Pharmacology Studies

Safety Pharmacology, one of disciplines of drug discovery and development, evaluates potential risk of new pharmaceutical entity and establishes whether these changes may pose a liability. These studies are aimed to characterise the pharmacodynamic/pharmacokinetic relationship of a drug's adverse effects using modern methodology. ICH S7A and S7B guidelines are the basis for regulatory safety pharmacology studies. ICH S7A recommends a particular focus on physiological systems (viz., CVS, Respiratory, & CNS), which are critical for life. Evaluation of effect on these systems is considered to be critical in safety pharmacology studies. Changes in respiratory function should be assessed with the same scientific rigourness, as the CNS and cardiovascular systems.

Many pharmaceutical drugs are known to adversely affect the respiratory function. Incidence of drug induced respiratory disorders is low but is associated with a high mortality. Respiratory related adverse event is only 0.5%–1.2% of total adverse events of drugs but that attributes to 12.3% of life threatening drug-induced disease and 25%–30% deaths[1]. This may be ascribable to the high blood flow, received by lungs. Respiratory safety studies are further supported by the fact that many patients, those involved in trials or under treatment, have a compromised respiratory function. The safety concern arising, on administration of drugs to patients with pulmonary disorder, because drugs producing non-significant effect in the healthy subjects, may be life threatening, e.g., β- blockers in asthmatic patients and respiratory depressants in patient with sleep apnea[2]. These acute fatal changes are the primary reason for evaluating new drugs on respiratory function in animal models and should be performed prior to initiation of clinical trials[3].

Respiratory safety pharmacology studies are performed to evaluate the potential of drugs to cause secondary pharmacologic or toxic effects that impact respiratory function. Respiratory function can be altered due to changes in pumping apparatus or in the mechanical properties of lungs[4]. Therefore, the evaluation of respiratory function can completed by evaluation of both functional components, i.e., pumping apparatus and lungs. In these studies, drug induced changes in ventilatory patterns of intact conscious animals, evaluated first and followed by effects, on the mechanical properties of lungs, in anesthetised/paralysed animals. These studies provide idea whether these changes are in the total respiratory system or related to pulmonary or extra-pulmonary factors. The drug induced effect on ventilatory function can be evaluated by using parameters, viz., respiratory rate, tidal volume, minute volume, peak inspiratory flow, peak expiratory flow, and fractional inspiratory time. Effect on mechanical properties of lungs can be evaluated in animal models by performing flow-volume and pressure-volume maneuvers. Parameters for airway obstruction detections are peak expiratory flow, forced expiratory flow at 25 and 75% of forced vital capacity, and a timed forced expiratory volume. For lung restriction detection the parameters are total lung capacity, inspiratory capacity, functional residual capacity, and compliance.

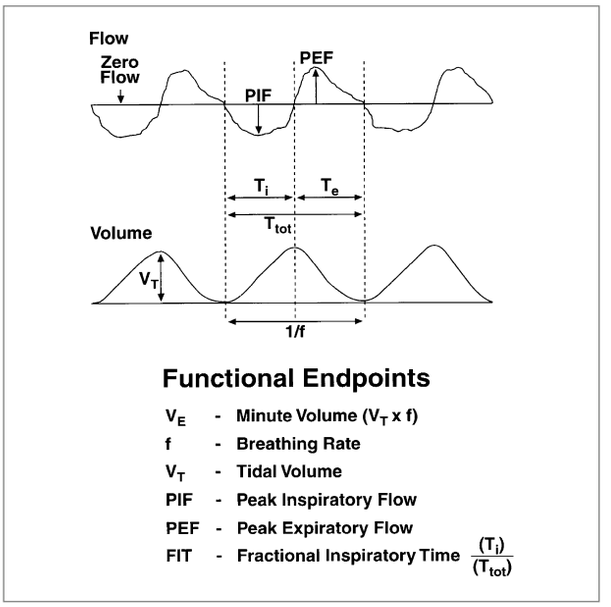


Fig. 1: Tracings of lung airflow and lung volume changes during spontaneous breathing in a conscious rat[5]

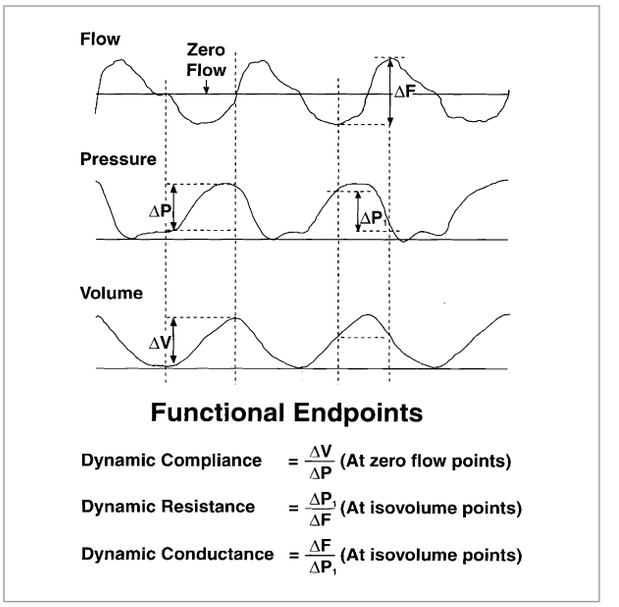
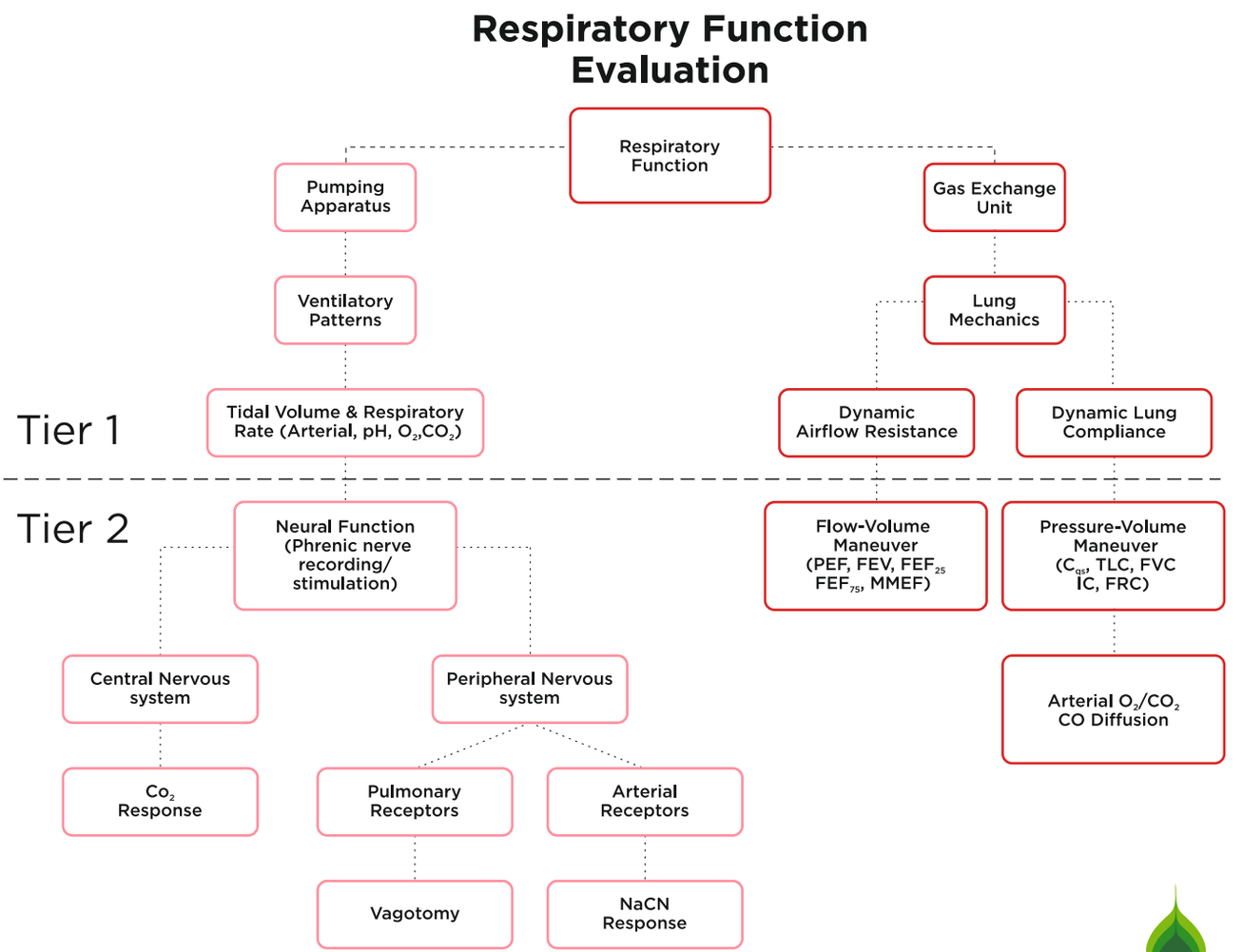


Fig. 2: Tracings of lung airflow, transpulmonary pressure, and lung volume changes during spontaneous breathing in a rat[5]

Flow chart showing the strategy for evaluating drug-induced effects on respiratory function [5]. Tier 1 tests are conducted to detect and quantify functional changes of the respiratory system, while Tier 2 tests are conducted to investigate mechanisms or further characterise effects associated with a functional change.



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About The Author

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Having more than 8 years of experience in performing various safety pharmacology and repeated dose toxicity studies in compliance with GLP.

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