FORCED EXPIRED VOLUME MEASUREMENTS IN PRECLINICAL MODELS OF RESPIRATORY DISEASE

THIS DOCUMENT OUTLINES THE IMPORTANCE OF TRANSLATIONAL FORCED EXPIRED VOLUME MEASUREMENTS IN PULMONARY DISEASE MODELLING

KEYWORDS: Spirometry, Asthma, Pulmonary Fibrosis, Emphysema, Cigarette, E-cigarette, Pollutant Exposure

Respiratory diseases pose substantial challenges to global public health, necessitating a comprehensive understanding of their underlying mechanisms and potential therapeutic interventions. As researchers strive to bridge the gap between preclinical investigations and clinical outcomes, the accurate assessment of Forced Expired Volume (FEV) and Forced Vital Capacity (FVC) emerges as a cornerstone for establishing translational relevance.

The flexiVent FX can be easily equiped with the FEV extension (Figure 1) to provide a complete and comprehensive lung function phenotype of any pulmonary disease model. This application note highlights the invaluable role of the FEV extension's measurements in the translation of preclinical findings into tangible benefits for human respiratory health.

Figure 1 - The flexiVent FX equipped with the FEV Extension

1. ASTHMA

In asthma, airway obstruction and inflammation are key features, causing narrowing of airways and decreased airflow. Monitoring FEV and FVC helps assess the extent of this obstruction and the responsiveness of bronchial smooth muscles. In the literature, various mouse models of asthma have shown a significant decrease in FEV and FVC following methacholine challenges, indicative of airflow restriction[1,2].

Bronchodilators are a cornerstone of asthma treatment, providing quick relief by relaxing bronchial smooth muscles and improving airflow. By measuring changes in FEV and FVC before and after administering bronchodilators such as mepenzolate in animal models, researchers can evaluate the responsiveness of the airways to such treatments[3].

FEV and FVC measurements also enable researchers to evaluate the efficacy of candidate drugs such as Dupiluimab or interventions in improving lung function and reducing airway inflammation[4]. Dupiluimab has been shown to have a protective role on the FEV lung function decline in preclinical asthma models[4]. These positive outcomes in animal models can guide the development of new asthma treatments.

2. PULMONARY FIBROSIS

Pulmonary Fibrosis involves the accumulation of scar tissue in the lungs, which leads to impaired lung function. Mouse models of fibrosis typically exhibit a restrictive profile, with a reduced FEV,

FVC, and Peak Expired Volume (PEF)[1,5]. Experimental treatments resulting in improvements of these parameters can provide a strong rationale for advancing treatments to clinical trials. For instance, recent studies confirmed the therapeutic impacts of ALK5 inhibition through improved FEV in their mouse model of pulmonary fibrosis[6].

Monitoring FEV and FVC in conjunction with histological, molecular, and imaging analyses can help correlate changes in lung function with specific pathological features, such as fibroblast activation, collagen deposition (hydroxyproline), and inflammation [1,5,7] as in Figure 2. This helps to better understand the relationship between structural changes and functional impairment.

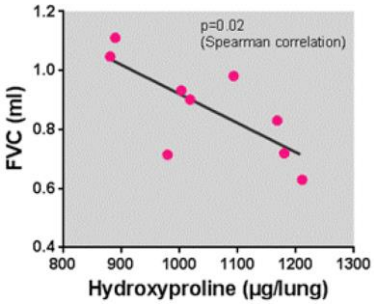

Figure 2 - Correlation between FVC vs lung hydroxyproline in bleomycin-exposed mice[4]

3. EMPHYSEMA

Emphysema is a type of chronic obstructive pulmonary disease (COPD) characterized by the destruction of lung tissue, leading to reduced lung function. Monitoring FEV and FVC in animal models enables researchers to quantitatively assess the extent of lung function and airflow impairments, which are hallmarks of emphysema.

Emphysematous mice display a decrease in FEV and PEF; characteristic of an obstructive phenotype as seen in Figure 3[1,8,9]. Changes in these parameters can help researchers understand how emphysema evolves and determine the most appropriate time points for intervention studies.

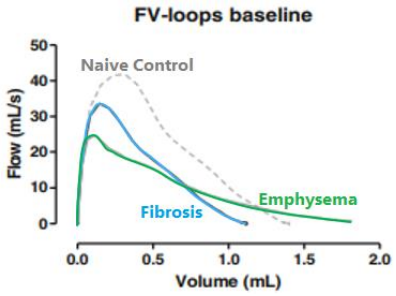

Figure 3 - Flow Volume Loops in bleomycin fibrosis model compared to PPE emphysema model[1].

Recent studies have examined novel innovative strategies for addressing pulmonary emphysema, leveraging the flexiVent FEV to yield insightful translational data. In a first study, the therapeutic viability of AM80-encapsulated nanoparticles was explored within an elastase-induced mouse model of COPD[10]. The administration of Am80 resulted in notable enhancements in respiratory function (FEV). Another study investigated the effects of CBD-FGF2 treatment on various lung function parameters, lung capacities, FEV and static compliance, across distinct groups[11]. Remarkably, mice subjected to CBD-FGF2 displayed marked improvements in lung capacity, when compared to the untreated group. These studies highlight the potential of both Am80 and CBD-FGF2 therapies in mitigating compromised lung function within COPD mouse models.

4. SMOKE EXPOSURES

Cigarette and e-cigarette exposure can lead to airway inflammation, mucus production, and impaired lung function. Monitoring of FEV and FVC in animal models post-smoke exposure helps researchers understand how sustained exposure contributes to persistent changes in lung function and the development of chronic respiratory conditions.

In recent studies, exposure to cigarette, IQOS or e-cigarette smoke had a negative impact on lung function and flow parameters (FEV, FVC) in murine models of smoke exposure[12,13,14]. Other

studies even explored maternal e-cigarette vapor exposure, uncovering persistent lung dysfunction (decreased FEV) and structural impairments in adult offspring, demonstrating the lasting influence of *in utero* exposure to e-cigarette vapor[14].

5. INFECTIOUS DISEASE

Infectious diseases, particularly those affecting the respiratory tract, can cause various degrees of lung inflammation, edema, and tissue damage. Monitoring FEV and FVC in these models provides a direct way to quantify the functional consequences of these infections on the respiratory system.

In a recent preclinical study of pneumonia, microRNA-based regenerative therapy was introduced as a novel approach to microbial infection treatment. In *Streptococcus pneumoniae* infected mice, miRNA-302 treatment improved lung function (FEV, FVC), aiding host recovery as seen in Figure 4[15]. Additional studies have seen a similar decline in FEV/FVC in preclinical models of coinfected influenza virus and *Haemophilus influenzae*[16].

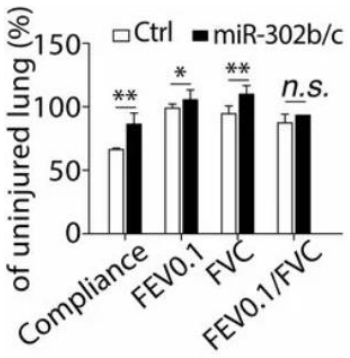

Figure 4 - miR-302 improves lung function measurements such as Compliance, FEV and FVC[15]

6. POLLUTANT EXPOSURE

Environmental pollutants, including particulate matter, ozone, and volatile organic compounds, can lead to airway inflammation, oxidative stress, and reduced lung function. A decline in lung function parameters including FEV and FVC have been reported in preclinical models of inhaled arsenic, carbon black, ozone, cobalt and diesel exhaust particles[17,18,19,20].

Research on pollution-related health effects, supported by lung function data, can be used for educational purposes to raise public awareness about the risks of pollution exposure and promote behavior changes that reduce exposure.

7. CONCLUSION

In conclusion, FEV and FVC measurements in animal models of respiratory disease play a pivotal role in understanding disease mechanisms, evaluating severity, testing interventions, and establishing translational relevance. These parameters from the flexiVent FEV extension provide quantitative data that help researchers bridge the gap between basic research and clinical practice, contributing to the development of novel treatments and improved patient care.

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