Course Name: Pulmonary Function Test -Interpretation and Application in clinical practice

Professor Name: Dr R. Arunkumar

Department Name: Pharmacology

Institute Name: Chettinad Hospital and Research Institute

W2_L3_Drug Effects on Pulmonary Function

Good morning. I am Dr. Arun Kumar, Vice Principal and Professor and Head of the Department of Pharmacology at Chettinad Hospital and Research Institute. I will be talking about Drug Effects on Pulmonary Function. I have divided this topic into four categories. First, I will be talking about drugs which are directly acting on the respiratory tract or lungs and then affecting the lung function. And then I will be talking about drugs which are acting on brain. We call them centrally acting drugs. These medications or drugs act on the respiratory center in the lower pons and medulla and then affecting the lung function. And then general anaesthetics, we all know that these medications are going to depress or suppress all the active centers of brain. And these medications are also affecting the pulmonary function, we will be talking about them.

And finally, adverse effects of drugs. Drugs can also cause injury to the lung, parenchyma or the alveoli or the bronchus and these are called as drugs that are causing drug induced lung injury. To start with, when we talk about drugs that are acting on lungs or respiratory tract, we mainly have two categories of drugs in this. One is drugs for cough and then we have asthma.

We will study the drugs for asthma in detail in the later slides. And when we focus on drugs that we use to treat cough, we know, that cough sometimes hurt individuals. There are two types of coughs, one is the productive cough or we call it wet cough, in which the patients will try to expectorate the sputum, the infected material or sometimes it is non-infected material from their throat or from their respiratory tract, they try to expectorate and then spit it. So, when we have severe cough, it disturbs us. So, we try to use medications to treat this cough and for wet cough, a productive cough, we try to use mucolytics or secretion enhancers.

What are mucolytics? These are medications or drugs which liquefy the sputum which is so thick. The sputum or the infected material in the respiratory tract is so thick that we try to expectorate and we find it difficult to expectorate and then spit. And when we use mucolytics, these drugs will liquefy the thick sputum and thereby, we can easily

expectorate the sputum which was previously thick and now has become little liquid or thin. The drugs are Bromhexine, Ambroxol and Acetyl cysteine.

We also have drugs called secretion enhancers. We use them in productive cough as well. The drugs are sodium or potassium citrate, potassium iodide, Guaiphenesin or Ammonium chloride. These medications, they increase the secretion in the respiratory tract, thereby they try to help the thick sputum to get little liquidated so that we can easily expectorate them. On the contrary, we have drugs like, Codeine or Pholcodeine - these are all opioid medications. We also have non-opioid medications like Noscapine or Dextromethorphan. These medications are called cough suppressants. These drugs do not act in the periphery or in the lungs or respiratory tract. They go to the brain, there is a respiratory, I mean cough center I was talking about and they suppress the cough center, thereby they reduce this cough. We do not use these medications in productive cough, we use them only in chronic cough or allergic cough where we do not suspect infection, but then these patients are suffering with cough for a longer time and hence we will be using these medications to suppress cough.

And firstly, these medications that we use for cough, they do not significantly affect the pulmonary function or lung function. And hence when a patient is going for pulmonary function tests, these medications they do not affect their lung function. Whereas when we use these medications, drugs for asthma, asthma is a disease, it is an airway disease, it is an inflammatory disease, there is inflammation of the airway giving us problems like wheezing or cough, breathlessness, they also impact their quality of life significantly.

Bronchial asthma: The basic pathology is that there is inflammation and this inflammation of bronchial mucosa or airway mucosa is going to release a lot of inflammatory mediators which are going to affect the bronchus, the mucosa, the submucosa, and the smooth muscle and resultantly the smooth muscle will go for contraction leading to bronchospasm or bronchial constriction and these patients will suffer with bronchial asthma. And when we treat bronchial asthma, we will be using two categories of medications. One category of medications are called bronchodilators. These bronchodilators will dilate the bronchial smooth muscle, will relax the bronchial smooth muscles so that these patients can breathe comfortably. They give symptomatic relief, very important symptomatic relief to those patients who are suffering with bronchial asthma, we have beta receptor agonists, we have methylxanthines and then we have anticholinergics. Beta receptor agonists because we know well that the bronchial smooth muscle has got receptors like muscarinic receptors, M3 type and then beta receptors, B2 receptor subtype. When we stimulate beta 2 receptors in the bronchial smooth muscle, it causes relaxation of the bronchial smooth muscle. And hence we are using beta 2 receptor agonists like Salbutamol, Terbutaline. We have medications like Salmeterol and Formoterol. The initial two medications like Salbutamol and Terbutaline, they are short-acting beta agonists. They act only for 4 to 6 hours. Whereas Salmeterol and Formoterol, they are long-acting medications. They act for more than 12

hours. They are called long-acting beta agonists, LABA. The initial drug Salbutamol and Terbutaline, they are called short-acting beta agonists, SABA. These medications stimulate beta 2 receptors and they increase the width of the bronchus and thereby they help the patients to breathe comfortably.

Whereas if you look at the anticholinergics, I have told that in bronchial smooth muscle, we also have muscarinic receptors, M3 type receptors. Acetylcholine is the primary neurotransmitter and when acetylcholine is stimulating M3 receptor, it causes contraction of the smooth muscle leading to bronchoconstrictions. And hence we will be using, when we want to treat bronchial asthma, we will be using anticholinergics or muscarinic receptor antagonists. We have two drugs at least that I have listed here, Ipratropium bromide and then Tiotropium bromide. These medications block M3 receptor and thereby they produce bronchodilatation. They help the patients who are suffering with wheeze in bronchial asthma.

Then we have methylxanthines, we have Theophylline, Aminophylline and then Doxophylline, these compounds are present naturally in coffee and tea. The beverages that we commonly consume, maybe in the morning or maybe during the daytime, these are methylxanthines. They also help us dilate the bronchus. They also help us relax the bronchial smooth muscles and help us in overcoming the bronchoconstriction. Talking about other drugs that we use in bronchial asthma, they are not as such bronchodilators. They do not give us much symptomatic relief initially, but over the period when we use them on a long-term basis in bronchial asthma, they help to reverse the disease pathology. They are called anti-inflammatory medications or immune modulatory medications that help us overcome the disease pathology. The basic disease pathology is airway hyper-responsiveness to common things like pollutants or some infective organisms or mites or even psychologically we get some triggers. We call them as triggers. So, these medications will overcome our responsiveness or hyper-responsiveness to some of the triggers. We have leukotriene antagonists like Montelukast, Zafirlukast and then we have mast cell stabilizers, Sodium Chromoglycate or ketotifen. Then we have corticosteroids. We use them systemically also like Hydrocortisone or Prednisolone or at present we are using inhalational corticosteroids like Beclomethasone or Budesonide, Fluticasone or Ciclesonide. And then we also have a monoclonal antibody. They are called biological agents, Omalizumab. We have seen that bronchial asthma, there is hypersensitivity reaction. There is hyper-responsiveness of the airway mucosa to the triggers. By using Omalizumab we can block IgG, I am sorry IgE. This is one of the antibodies which is basically responsible to trigger this hypersensitivity reaction and hence when we use this Omalizumab we can block the IgE and this is not useful in all the patients of bronchial asthma or only those patients who have got increased levels of IgE we can give benefit to those patients by blocking the IgE activity in their bronchial tree. I told we have two categories of medications in bronchial asthma, bronchodilators, and immune modulatory

agents. Immune modulatory agents as such can modulate the lung function on long-term use but bronchodilators even with one dose, they can modulate the lung function and they can influence the pulmonary function test.

Beta 2 agonists, methylxanthines and anticholinergics and I have told beta 2 agonists they are bronchodilators, they relax the bronchial smooth muscles but their activity is mainly restricted to or predominantly seen in smaller airways like smaller bronchus, branches of the bronchus, bronchioles and in bronchial asthma mostly we have the disease affecting the smaller airway and hence bronchodilators, beta 2 receptor agonists are very useful in bronchial asthma than the anticholinergics. Because anticholinergics they block M3 receptors and they are predominantly useful in relaxing or in dilating the larger airways and hence we will be using anticholinergics or their benefit is much more in chronic obstructive airway disease than in bronchial asthma and how do they cause this bronchial relaxation or bronchial muscle relaxation is that by binding to beta 2 receptors, a beta agonist they increase this enzyme activity adenine cyclase thereby they increase cyclic AMP levels and leading to reduction in the intracellular calcium thereby relaxing the airway. Whereas anticholinergics I have told that they will be acting mostly in the larger airways. When we look at methylxanthines they block phosphodiesterase enzyme. This enzyme when it is blocked, same mechanism like beta agonists, they increase the cyclic AMP inside the bronchial smooth muscle thereby they cause relaxation and then bronchodilatation.

They also have other non-specific mechanisms; one important mechanism is that methylxanthines, they also block adenosine receptors and thereby they produce bronchodilatation as well. Now these three categories of drugs when we subject any patient to pulmonary function, these three categories of drugs will mask in case if they have breathing difficulty in case if we are going to have abnormal pulmonary function if we use these medications, we can alter the real outcome of a pulmonary function tests and hence we need to be careful when we are using them in those patients when we subject them to pulmonary function tests. These medications improve the bronchial width and increase forced expiratory volume in one second (FEV1) and beta blockers like we have seen beta agonists they produce bronchodilatation and whereas, beta antagonists, beta blockers they block the beta receptors non-selective beta blockers especially like propranolol they block the beta 2 receptors to some extent in the bronchial airway and they may produce bronchoconstriction and they can also affect the pulmonary function and hence the point is that when we do pulmonary function tests we need to make sure that these patients are not taking beta agonists or beta blockers or anticholinergics or methyl xanthines. We need to be aware of those facts and hence we can avoid masking of the real pulmonary parameters with these medications.

Going to the other category of drugs, we have seen, when I started my presentation, I was talking about drugs acting on the respiratory tract and then affecting pulmonary function. Now I am moving to the drugs which are acting in the central nervous system of brain - in what way they are affecting the pulmonary function. We have two categories here; respiratory stimulants - these are medications acting on the respiratory centers in the brain they stimulate the respiratory centers and they increase the respiratory rate and they also increase the respiration per se. We do not use them very commonly in our clinical practice but there are conditions there are situations where we will be forced to use these medications like respiratory failure a severe respiratory depression chronic obstructive pulmonary disease or apnea in newborn we call it neonatal apnea. In those situations, sometimes we will use these respiratory stimulants to improve the respiration or respiratory drive we call it. This diagram is giving you some details about the respiratory center in the brain.

The respiratory center is not a single center it has got multiple areas or segments in the brain they are all located in the lower pons or maybe in the medulla predominantly. We have two drugs here caffeine the same caffeine that we we consume coffee and it is present in caffeine. Doxapram is the other drug. Caffeine it inhibits phosphodiesterase enzyme and it increases the intracellular cyclic AMP in the brain in the medulla and thereby it increases the respiratory drive respiratory rate is increased and the patients sometimes may go for tachypnea also. Doxapram it is another drug; it is a stimulant; it is stimulating chemoreceptors central chemoreceptors and peripheral chemoreceptors central chemoreceptors are in medulla in the respiratory center. Peripheral chemoreceptors are in the carotid arteries especially the internal carotid artery. By stimulating these receptors doxafram increases the respiratory drive it increases the respiratory rate also sometimes it causes tachypnea also the respiratory rate is increased more than desired also sometimes with doxapram and caffeine at high dose levels. Respiratory depressants or suppressants we call them we have medications which act on brain the respiratory center and they suppress the center they can cause a respiratory depression they can cause sometimes respiratory arrest and apnea also can be precipitated with these medications. The most common medication is opioid. Morphine they are all analgesics they are excellent analgesics we use morphine in myocardial infarction to reduce the chest pain and we have tramadol we use it in common painful conditions maybe in arthritis maybe muscular pain any painful condition we are using tramadol. Heroin is a drug of abuse. Fentanyl we use it in general anesthesia all opioids especially when we are using them intravenously or when people are abusing without knowing the real implications of using parental injections for getting the pleasure or euphoria they go for respiratory depression or sometimes respiratory arrest. All the sedatives and hypnotics like benzodiazepines, barbiturates, all the central nervous system depression drugs including general anesthetics or ethanol the common alcohol or liquor that we consume they are all respiratory suppressants and sometimes the

patients die also out of this respiratory suppression and in case if it is due to poisoning by benzodiazepines and if there is apnea or severe respiratory suppression we can use benzodiazepine antagonist like Flumazenil we can inject it intravenously to block the action of benzodiazepine on respiratory center and we can revive the patients. In case of opioid poisoning or opioid drug abuse and if there is a respiratory suppression, we can use opioid antagonists like Naloxone or Naltrexone we can inject them and we can revive the patients we can give them breathing or sometimes rarely when there is severe respiratory suppression, we have to use mechanical ventilation till the patients recover from the respiratory suppression.

Moving on to general anesthetics we know that we will be using these medications when we put our patients for surgery elective surgeries or emergency surgeries because we want to paralyze them, we want to make them unconscious general anesthesia is nothing but reversible unconsciousness we can call it reversible death in that way. All these general anesthetics are suppressants to brain, cerebrum, cerebral cortex, cerebellum, respiratory center, vasomotor center all the vital centers are suppressed by general anesthetic drugs. We have a lot of drugs we have if you see Nitrous oxide we are using them for long time and then we have ether which is a volatile liquid again for more than 200 years we are using ether to give general anesthesia but we do not use ether very commonly because it is an irritant. We use Halothane, Isoflurane, Sevoflurane, Desflurane we are using all these volatile liquids we are administering them inhalationally and then we do general anesthesia. Then we have intravenously administered anesthetic drugs like Thiopentone sodium we use it very commonly Propofol we are using it and Ketamine we are using it to give dissociative anesthesia, Benzodiazepines, Opioids all these medications we are using in general anesthesia and all of them are going to suppress respiratory center. All of these drugs reduce alveolar ventilation and perfusion. They affect pulmonary function tests they decrease minute ventilation they decrease respiratory rate and tidal volume; FEV1 it is reduced FRC is reduced functional residual capacity forced expiratory volume in one second everything is going to be reduced by general anesthetics we should be aware of it the activity of general anesthetics on pulmonary function when we do pulmonary function tests.

Now we are moving to the fourth category of drugs we have seen the drugs acting on respiratory tract we have seen centrally acting respiratory suppressants and stimulants and we have seen the effect of general anesthetics on pulmonary function tests. Moving on to drug induced lung injury we have been using a lot of drugs we have hundreds of drugs in our practice and many of these drugs can affect the lungs the bronchus the bronchioles smooth muscles, interstitium, parenchyma all these can be affected by the medications that we are using to treat other conditions. Now this drug induced lung injury can have interstitial inflammation and fibrosis the injury may be related to bronchospasm, bronchial smooth muscle constriction, pulmonary edema, pleural effusion many of these

things can happen when we are using medications in treating other conditions. The most common form of drug induced liver I mean I am sorry lung toxicity is drug induced interstitial lung disease I am again repeating most common form of drug induced lung toxicity is interstitial lung disease it affects the lung parenchyma or interstitium. In which route we administer the medications we get this ILD. Many times, when we administer the drugs orally or parentally there is a possibility of getting interstitial lung disease but sometimes or rarely even when we administer the drugs inhalationally the interstitium can get affected or sometimes intrathecally we administer the medications we can have the lungs or lung parenchyma getting affected. But not all patients are going for this complication there are some high-risk factors if the patients are associated with these high-risk factors, then the chances of going for lung injury is more in those patients. Extremes of ages and females, newborn is more prone to have lung injury, geriatric age group population this subset of population again is more prone to get into interstitial lung disease out of drugs. High dose of the medications that we use longer duration of administration of the medications the chances of ILD is more and if you use those medications or drugs along with high dose oxygen for a long time then the chance of ILD is more. If the patients are receiving radiation in addition to the medications, then they are more prone if they have pre-existing lung disease or drug interactions then all these are going to contribute to more risk of getting ILD with these medications. There are multiple mechanisms involved in this lung injury. The drugs can give direct cellular toxicity, interstitial inflammation, the alveolar epithelial cells can get affected, bronchial epithelial cells mucosal cells can get affected then hypersensitivity reaction we have seen IgE can play a role and inflammatory mediators like tumor necrosis factor, cytokines and interleukins all of them can play a role in this and oxidative stress.

And these injuries can lead to multiple pathological findings in ILD, hypersensitivity pneumonitis, organizing pneumonia, interstitial pneumonia, a rarely BOOP. What is BOOP? It is Bronchiolitis Obliterans Organizing Pneumonia and sometimes granulomatous pneumonitis. There are lot of drugs number of drugs can get associated with ILD starting from antimicrobial agents, anti-inflammatory drugs, biological agents, cardiovascular drugs, chemotherapeutic agents and miscellaneous drugs. The list is so exhaustive and so vast but I have tried to give you only a gist of common medications with which we can have ILD. Amphotericin B, antimicrobial agent we can see here amphotericin B, Isoniazid is a drug that we use for tuberculosis, Nitrofurantoin commonly used for urinary tract infection, Sulfasalazine, Sulfonamide all of them on long term use are associated with lung injury or ILD. Aspirin anti-inflammatory drug we use it and then we have other medications we use for treating rheumatic disorders or drugs involving rheumatology, rheumatoid arthritis, systemic lupus erythematosus, as Sjogren's syndrome like gold, penicillamine, Infliximab, Methotrexate, Etanercept all of them have got a risk of producing ILD.

Biologicals they are monoclonal antibodies they are used in many of the conditions in maybe in rheumatology or maybe in autoimmune diseases, maybe in malignancies we are using them Adalimumab, Bevacizumab, Cetuximab, Rituximab and Trastuzumab all of them are running a risk of producing ILD. Cardiovascular system drugs we are using them very commonly in our practice ACE inhibitors like Captopril, Enalopril, Lisinopril, Perindopril, AC inhibitors long term use sometimes they produce interstitial lung disease, Amiodarone, an anti-arrhythmic drug we commonly use - Procainamide, Flecainide, Hydrochlorothiazide, Statins we use to reduce blood cholesterol they may produce ILD. Chemotherapeutic medications we use them for treating a lot of malignancies, hematological malignancies or solid organ tumors, lung cancer, Bleomycin, Busulfan, Carmustine, Cyclophosphamide very many drugs. But I have highlighted the four medications which are most associated with ILD and then miscellaneous medications we have Bromocriptine, we use it in hormonal conditions endocrine disorders, Cabergolide, even bromocriptine we are using it in diabetes mellitus. These medications are associated with ILD, Carbamazepine, an anti-epileptic medication, Sirolimus, immunosuppressant medication, sometimes Phenytoin again an anti-epileptic medication these are all associated with ILD.

Just to highlight some of the salient points related to each of these categories chemotherapeutic drugs I have already highlighted the most commonly implicated drugs in lung toxicity among the anti-cancer medications we have Bleomycin, Carmustine, Busulfan and Cyclophosphamide. Busulfan toxicity is straight away related to the duration of administration of busulfan. Long term administration gives you more chances of getting into lung toxicity, 3 to 4 years usually it happens with busulfan. Cyclophosphamide it does produce lung toxicity depending upon the duration of action but then there is also early onset lung toxicity that we encounter with Cyclophosphamide. Cardiovascular drug I have told amiodarone is the most common drug associated with ILD, long term use amiodarone. We give tablet amiodarone to treat arrhythmias for long term. All the statins are associated with ILD it is not just seen with one particular statin and hence we call it a class adverse event of all statins is ILD. Though it is not very common but then we need to realize because many patients with cardiovascular disease they are going to take statins for long term maybe 5 years, maybe 10 years or 15-20 years we have seen patients are taking statins for such long term and hence if these patients are coming with unexplained breathlessness, we need to know it may be due to statin. Aspirin is the most common anti-inflammatory drug associated with ILD besides other anti-inflammatory and anti-rheumatoid drugs like I have already told that Gold, Penicillamine, Azathioprine and Methotrexate they are also associated with ILD. Antimicrobials, Nitrofurantoin very commonly used drug in urinary tract infection but then we use it only for 5 days and with this duration we do not run the risk of getting ILD but sometimes bedridden patients or people who are under Foley's catheter for a long term we give prophylaxis with Nitrofurantoin for months. In that

situation Nitrofurantoin may produce ILD. Besides Sulfonamides and Sulfasalazine and Amphidericin B and all these medications can give us interstitial lung disease.

Now what are the changes we can encounter in case if there is a drug induced ILD or drug-induced lung toxicity. Now usually in pulmonary function tests we have two patterns - one is a restrictive lung disease pattern the other one is obstructive lung disease pattern. Many times, we get pulmonary fibrosis we have interstitial lung disease we get a restrictive lung disease pattern in which we see that there is reduction in total lung capacity, reduction in residual volume and forced vital capacity is compromised and then diffusing capacity is also compromised. These are common changes that we encounter in those patients who are suffering with drug-induced ILD they have restrictive lung disease pattern but sometimes rarely we can have drug induced lung toxicity affecting bronchioles predominantly. We have Bronchiolitis obliterans-like changes and when we do pulmonary function tests in those individuals, we may not have restrictive lung disease pattern we may have obstructive ventilatory defect in them where we see reduction in the FEV1/FEC ratio reduction in FEV1 and then there is increased RV and RV/TLC ratio. These are all changes that we can encounter in drug induced ILD. Now how do we treat this ILD out of drug toxicity the prognosis is really guarded there is no guarantee that we treat them they may recover 100 percent but we try to withdraw the offending drug, we give them supplemental oxygen, there is a definite role for glucocorticoids and immunosuppressive drugs, though these medications are not useful in all the situations. Mortality, sometimes it happens, the mortality is very high in acute Amiodarone induced pulmonary toxicity where the risk is nearly 40 to 50 percent mortality.

Now with this I think I have come to the end of my presentation where I have tried to give a gist of the drugs and their effects on pulmonary function. I have tried to give four categories though I am repeating it I would like to repeat I have tried to capture some of the medications used they are targeting on lungs and respiratory tract like the drugs that we use in asthma and cough they may influence the pulmonary function and then I have listed a few drugs which are acting on respiratory center and then affecting the pulmonary function then a note on general anaesthetics and then drug induced interstitial lung disease. With this I am concluding my presentation on drug effects and pulmonary function. Thank you very much.