Presurgical Pulmonary Evaluation in Renal Transplant Patients

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Abstract

Patients with chronic renal failure (CRF) due to various mechanisms are prone to significant pulmonary comorbidities. With the improvements in renal replacement therapy (RRT), patients with CRF are now expected to live longer, and thus may develop complications in the lung from these processes. The preferred treatment of CRF is kidney transplantation and patients who are selected to undergo transplant must have a thorough preoperative pulmonary evaluation to assess pulmonary status and to determine risk of postoperative pulmonary complications. A MEDLINE®/PubMed® search was performed to identify all articles outlining the course of pre-surgical pulmonary evaluation with an emphasis on patients with CRF who have been selected for renal transplant. Literature review concluded that in addition to generic pre-surgical evaluation, renal transplant patients must also undergo a full cardiopulmonary and sleep evaluation to investigate possible existing pulmonary pathologies. Presence of any risk factor should then be aggressively managed or treated prior to surgery.

Keywords: Pre-surgical evaluation, Pulmonary complications, Pulmonary evaluation, Pulmonary hypertension, Renal transplant

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Introduction

The renal and respiratory systems work together to maintain the acid-base equilibrium in the body. Failure of one of these systems leads to a compensatory effect from the other which may be detrimental to one’s health. Patients with chronic renal failure (CRF), due to various mechanisms are prone to significant pulmonary comorbidities.1 With the improvements in renal replacement therapy (RRT), patients with CRF are now expected to live longer, and thus be at higher risk for the pulmonary complications that may arise. The preferred treatment of CRF is kidney transplantation.2 Patients who are selected to undergo renal transplant must have thorough pre-operative pulmonary evaluation to assess pulmonary status and to determine risk of postoperative pulmonary complications [Figure 1]. In addition to general pre-surgical issues, pulmonary complications of CRF patients include pulmonary edema and pleural effusions, which are attributed to reduced fluid clearance (fluid overload) and an increase in pulmonary vasculature permeability.3 Other less common complications include pulmonary hypertension,4 pulmonary fibrosis,5 and pulmonary calcifications6 [Table 1]. It is important to identify these patients and make sure that they are treated more aggressively as postoperative pulmonary complications in non-thoracic surgery patients have been seen in 2-19% of patients.7 Risk factors involved in renal transplant surgery may be classified as 1) patient-related risk factors and 2) procedure-related risk factors. For the purpose of this review, focus will be placed on modifiable and manageable risk factors arising from the patient. Risk factors that may contribute to postoperative pulmonary complications include smoking, poor over health status, age, obesity, chronic obstructive pulmonary disease and...
asthma.\textsuperscript{[8]} In addition focus will be placed on specific pulmonary pathologies with their etiologies being the renal system.

The aim of this review is to outline the pre-surgical evaluation in renal transplant patients as well as outline the possible pulmonary complications in CRF patients. A MEDLINE®/PubMed® search was performed with the objective of identifying all articles published in the English language between January 1950 and May 2014 with “Pre-surgical pulmonary evaluation” in the title. Combinations of medical subject heading terms including “Pre-surgical evaluation,” “Surgery in renal failure patients,” “Pulmonary complications of surgery” and “Pulmonary complications in renal failure” were used. We largely selected publications from the last 20 years, but did not exclude older publications that were widely referenced and highly regarded. We also searched the reference lists of articles identified by this search strategy and selected those we judged to be relevant. All pertinent reports were retrieved and the relative reference lists were systematically searched in order to identify any potential additional studies that could be included. All data was accessed between January and May 2014.

**Pre-Operative Pulmonary Evaluation**

Patients undergoing elective surgical procedures routinely undergo general health assessment prior to surgery. In the case of renal transplantation the same holds true. Certain modifiable risk factors should be assessed and addressed to ensure minimal postoperative complications [Figure 1].

**General health**

Overall general health has become a good indicator of possible post-surgical complications. Indices of risk such as the Goldman cardiac-risk index (which assesses factors from the patient’s history, the physical examination, and laboratory data) is a good indicator

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* Smoking cessation for > 6 wks if current smoker; short acting Beta 2 agonist and systemic corticosteroid treatment for bronchial reactivity

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**Table 1: Pulmonary complications of renal disease**

| Pulmonary presentation    | Renal etiology                                      |
|---------------------------|-----------------------------------------------------|
| Pulmonary Edema           | Acute and chronic renal failure                     |
|                           | Hemodialysis                                        |
|                           | Renal transplantation                                |
| Pulmonary hypertension    | Chronic renal failure                                |
| Pleural effusion          | Acute and chronic renal failure                      |
|                           | Hemodialysis                                        |
|                           | Renal transplantation                                |
|                           | Peritoneal dialysis                                  |
| Metastatic pulmonary      | Chronic renal failure                                |
| calcification             | Hemodialysis                                        |
|                           | Renal transplantation                                |
| Obstructive sleep apnea   | Chronic renal failure                                |
|                           | Hemodialysis                                        |
|                           | Peritoneal dialysis                                  |
| Infections                | Acute and chronic renal failure                      |
|                           | Hemodialysis                                        |
|                           | Renal transplantation                                |
| Lymphoma/Lung cancer      | Renal transplantation                                |
|                          | Hemodialysis                                        |
| Hypoxemia                 | Pulmonary edema                                      |
|                           | Pleural effusion                                     |
|                           | Pulmonary calcification                              |

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**Figure 1:** Management protocol pulmonary evaluation in renal transplant patients
of the general risk of a surgical candidate as well as cardiopulmonary complications." It has also been observed that poor exercise tolerance is an indicator of postoperative pulmonary risk. In a multivariate analysis of patients over 65 years of age who were undergoing abdominal or non-rective thoracic surgery, the inability to perform two minutes of supine bicycle exercise sufficient to raise the heart rate to 99 beats per minute was the strongest predictor of pulmonary complications. The inability to exercise was predictive of a 79 percent incidence of pulmonary complications; only 33 percent of patients without pulmonary complications were unable to exercise. It is important that all transplant candidates have a complete medical checkup from their primary care physician as well as relevant specialists.

Smoking
It has been well demonstrated that smoking is a modifiable risk factor for patients undergoing elective surgery. According to a study by Bluman et al., smokers experienced significantly more postoperative pulmonary complications than past or never smokers. Wellman and Smith found that the incidence of postoperative pulmonary complications following upper abdominal and thoracic surgery was doubled in cigarette smokers, and that smoking more than 20 cigarettes per day was associated with a fourfold increase in postoperative atelectasis. Wightman reported postoperative pulmonary complications in patients undergoing abdominal surgery to be 14.8% among smokers, as compared with 6.3% among never smokers. A prospective study of 200 smokers preparing for coronary bypass surgery found that there was a lower risk of pulmonary complications among those who had stopped smoking at least eight weeks before surgery than among current smokers (14.5 percent vs. 33 percent).

Smoking cessation
Due to the detrimental effects that smoking has on general health, it is important to make an effort to promote smoking cessation in chronic renal disease patients. Both non-pharmacologic and pharmacologic interventions are available for patients who are chronic smokers and are candidates for renal transplant. Evidence suggests that a combination of psychosocial counseling and pharmacotherapy be utilized including therapies such as bupropion, varenicline and nicotine replacement therapy (NRT). The use of these medications can increase an individual’s chance of abstinence. A combination of counseling and pharmacotherapy may achieve the highest abstinence rates.

Non-pharmacologic therapies
Several counseling methods, including counseling by health professionals, telephone quit lines, individual counseling, group counseling, and computer program or internet counseling have demonstrated efficacy. It is recommended that advice to quit and brief counseling be performed by a health professional at any or all contact with a smoker to help facilitate the quitting process. Intensive interventions, with person-to-person communication for four or more sessions may be more effective to achieve smoking abstinence than other non-pharmacologic methods. In the setting of CRF, personal contact by dialysis health care professionals makes the dialysis unit an ideal setting for smoking cessation interventions.

Pharmacologic intervention
The first step in pharmacologic management is over the counter pharmacotherapy which is composed of nicotine replacement therapy. NRT aids with physiologic nicotine withdrawal by simulating nicotine levels inhaled from smoking. NRT is available in a variety of products, including gum, lozenges, patches, and inhalers. Dosing of these therapies is based on the average number of cigarettes smoked per day. Dosing parameters differ for each NRT product. Smokers with CKD may use the usual doses of NRT, and experience similar adverse effects to nicotine as individuals with normal renal function.

Prescription medications for smoking cessation include bupropion and varenicline. Bupropion is a dopamine and norepinephrine reuptake inhibitor that increases dopamine activity. Patients who have not quit after seven weeks of therapy are considered to be non-responsive. Contraindications to bupropion use include alcohol abuse, previous seizures and history of head trauma, stroke, or brain injury because of bupropion’s ability to decrease the seizure threshold (Product Information: Zyban*, bupropion, 2008).

Varenicline is another option for smoking cessation and is a partial agonist/antagonist at the alpha-4 beta-2 nicotine receptor. Safety in patients with serious psychiatric illness such as schizophrenia, bipolar, and major depression has not been established. Individuals taking varenicline are 1.7 times more likely to quit than those taking nicotine replacement therapy. There has been anecdotal reports of varenicline associated renal failure. Close follow up with smokers initiating therapy with bupropion or varenicline is necessary to determine if patients are experiencing any psychiatric side effects. Both these drugs are excreted renally and dosing should be carefully monitored in the kidney transplant population. The doses of both varenicline and bupropion must be reduced as kidney function decreases. In addition it is important to realize that many of these patients may be on immunosuppressive therapy such as cyclosporine.
which may lead to increased concentration and increased risk of seizures with Bupropion use. As for possible drug interaction with tacrolimus it should be expected that, until further data are available, drugs that interact with cyclosporine may also interact with tacrolimus.\textsuperscript{[19]}

**Obesity**

Obesity has been recognized by the American Medical Association as a disease state and is a risk factor for all surgical patients. Obesity is defined as a BMI greater than or equal to 30 kg/m\textsuperscript{2} and has been shown to cause post-transplant surgical complications, delayed graft function\textsuperscript{[20]} and has demonstrated a negative effect including graft failure within the first year post-transplant.\textsuperscript{[21]} A recent study by Hoogeveen and colleagues showed that one year after transplant, BMI and BMI increments were both significant risk factors for mortality and graft failure in the long term.\textsuperscript{[22]}

Excess abdominal fat (central or visceral obesity), which is found above the waist, is related to increased risk of diabetes, heart disease as well as postoperative pulmonary complications. In men a waist greater than 40 inches and in women 36 inches is of concern. From a pulmonary point of view obesity leads to decreased lung volumes after surgery and is a principal cause of postoperative pulmonary complications. Morbid obesity causes a restrictive ventilatory pattern and decreases thoracic compliance and may lead to alveolar hypoventilation.\textsuperscript{[23]} Patients who are active on the renal transplant list should have their obesity addressed through lifestyle and diet modifications. If these patients are able to endure physical activity a regimen should be drafted to further aid weight loss.

**Obstructive Sleep Apnea (OSA)**

Obstructive sleep apnea is defined as the occurrence of at least five apneas/hypopneas (temporary cessation of breathing) in one hour.\textsuperscript{[24]} Symptoms typically associated with OSA include snoring, excessive daytime somnolence, and restless sleep. Male gender, smoking and alcohol consumption, obesity and aging are known factors associated with a higher propensity for OSA.\textsuperscript{[24]} OSA is associated with a number of medical comorbidities including hypertension, heart failure, myocardial infarction, diabetes mellitus, gastroesophageal reflux disease, stroke and CRF.\textsuperscript{[25,26]}

There is a strong association between CRF and OSA and sleep studies in end stage renal disease (ESRD) patients have identified increased prevalence of sleep apnea, both obstructive and central in origin.\textsuperscript{[27]} Consequences of sleep apnea such as increased renal sympathetic activity, intermittent hypoxia, hypertension, accelerated atherosclerosis, production of post-inflammatory cytokines, endothelial dysfunction and proteinuria may contribute to the progression of CRF. ESRD patients with OSA on peritoneal dialysis (PD) have lower nocturnal arterial oxygen saturation during nights on PD than on other nights; hence, PD may also adversely affect cardiovascular risk.\textsuperscript{[28]}

All patients with OSA should undergo a continuous positive airway pressure (CPAP) titration. The regular use of CPAP may prevent the progression of nephropathy by ameliorating glomerular hyperfiltration.\textsuperscript{[29]} Long-term CPAP reduces blood pressure and plasma renin and angiotensin II levels.\textsuperscript{[25,30]} Life style changes, alteration of sleep hygiene parameters and reduction of obesity have a significant role in reducing overall OSA severity and associated vascular risks, these strategies are often difficult to offer and monitor in patients with CRF.\textsuperscript{[31]}

Both anesthesia and postoperative analgesic measures can negatively affect OSA outcomes. The effects of anesthesia, sedation, and analgesics may work similarly, increasing the risk of detrimental effects to patients with OSA. The potential perioperative risks to OSA patients include increased morbidity and mortality, as well as difficult intubation and postoperative respiratory distress/obstruction.\textsuperscript{[32]} Patients may have to be initiated postoperatively on CPAP after the extubation process.

**Pulmonary function testing**

Pulmonary function testing is conducted on all patients who are to undergo a major surgical procedure. In the elective setting patients who are scheduled to undergo renal transplantation a full pulmonary assessment should take place. Pulmonary function may be abnormal in CRF patients due to various mechanisms such as fluid overload, infections, pleural effusions, pulmonary hypertension.\textsuperscript{[33]} It presents as a restrictive lung defect with a decrease in diffusion capacity of carbon monoxide (DLCO). Decreased DLCO may be due to anemia, pulmonary hypertension or concomitant restrictive ventilatory defect.

Up to 88\% of CRF patients showed pulmonary function abnormalities which improved significantly after transplantation. Improvement was seen in mean vital capacity and small airways small airways, as shown by low maximal mid-expiratory flow rates, which tended to improve after renal transplantation.\textsuperscript{[34]}

**Pulmonary Complications of Chronic Renal Disease**

**Hypoxemia**

In uremia, in addition to a loss of excretory function of the kidney, the metabolic and endocrine functions,
which involve all organ systems of the body, are affected. The pulmonary abnormalities seen in uremia include pulmonary edema, pleural effusions, pleurisy, pulmonary fibrosis, pulmonary calcification and respiratory muscle myopathy.\[34\]

These conditions lead to diminished pulmonary function and may alter respiration. Some alterations in pulmonary function may be a reduction in vital capacity (VC), decreased expiratory flows, decreased respiratory muscle strength and hypoxemia.\[33\] Patients with ESRD on RRT can have recurrent episodes of hypoxemia due to partial blockage of the pulmonary capillary bed by white cells\[35,36\] or silicone microemboli.\[37\] As mentioned above, the improvement is observed in mean vital capacity and small airways, as shown by low maximal mid-expiratory flow rates, which tends to improve after renal transplantation.\[34\]

### Pulmonary edema and pleural effusions

Patients with ESRD may experience many pleuropulmonary problems such as pulmonary edema and pleural effusions. Diseases such as systemic lupus erythematosus (SLE) may be associated with renal and pleural manifestations.\[38\] Another possible cause of these manifestations is that CRF patients are oliguric or anuric. This patient population also has an increased risk of ischemic cardiac disease and the possibility of cardiomyopathies.

### Pulmonary Hypertension (PHTN)

Pre-operative assessment must include evaluation for pulmonary hypertension as studies have indicated that it is an independent predictor or mortality in CRF especially those receiving RRT.\[39\] PHTN is felt to be a relative contraindication to renal transplantation in patients with CRF as it has been associated with increased early renal allograft dysfunction\[40\] and is also associated with reduced patient survival after transplant.\[41\]

Pulmonary hypertension is a multietiological disease defined as a mean pulmonary artery (PA) pressure ≥25 mm Hg and pulmonary arterial hypertension (PAH) has the extra criteria of a pulmonary capillary wedge pressure being ≤15 mm Hg [Table 2]. It is a chronic, progressive condition of pulmonary vascular remodeling, leading to right heart failure and ultimately death if left untreated.\[42\] Pulmonary hypertension in CRF patients is typically associated with left heart disease. Patients with CRF often also have a variety of risk factors predisposing them toward pulmonary venous congestion, including systemic hypertension, left ventricular hypertrophy (LVH), ischemic heart

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**Table 2: World health organization’s classification of pulmonary hypertension — Nice**\[42\]

| Group I - Pulmonary arterial hypertension |
|------------------------------------------|
| Idiopathic PAH                           |
| Heritable (BMPR2, ALK1, Endoglin, Unknown) |

| Familial disorder                      |
|----------------------------------------|
| Related conditions                     |
| Collagen vascular disease              |
| Congenital systemic-to-pulmonary shunt |
| Portal hypertension                    |
| Human immunodeficiency virus infection |
| Schistosomiasis                        |
| Drugs and toxins (Aminorex, Fenfluramine, Dexfenfluramine) |
| Pulmonary veno-occlusive disease       |
| Persistent pulmonary hypertension of the newborn |

| Group II - Pulmonary venous hypertension |
|-----------------------------------------|
| Systolic dysfunction                    |
| Diastolic dysfunction                   |
| Valvular disease                        |

| Group III - Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia |
|----------------------------------------------------------------------------------------------------------|
| Chronic obstructive pulmonary disease                                                             |
| Interstitial lung disease                                                                         |
| Sleep-disordered breathing                                                                       |
| Alveolar hypoventilation disorders                                                                |
| Chronic exposure to high altitudes                                                                |
| Neonatal lung disease                                                                             |

| Group IV - Pulmonary hypertension resulting from chronic thrombotic and/or embolic disease (CTEPH) |
|----------------------------------------------------------------------------------------------------|

| Group V - Pulmonary hypertension resulting from disorders directly affecting the pulmonary vasculature |
|--------------------------------------------------------------------------------------------------------|
| Inflammatory conditions                                                                           |
| Hematological disorders: myeloproliferative disorders, splenectomy                                  |
| Systemic Disorders: sarcoidosis, neurofibromatosis, lymphangioleiomyomatosis                        |
| Others: tumoral obstruction, chronic renal failure on dialysis, fibrosing mediastinitis              |
disease (WHO Group II Pulmonary Hypertension), and left ventricular (LV) diastolic dysfunction. Effort should be maintained to stabilize underlying cardiac condition prior to surgery. In patients with pulmonary hypertension elevated mean right atrial pressure, decreased cardiac index and elevated mean PA pressure are associated with a poor prognosis.

In PAH patients (WHO Group I Pulmonary Hypertension) treatment needs to be optimized and monitored. This population tends to be on phosphodiesterase-5 inhibitors (sildenafil, tadalafil) or on a combination of endothelin receptor blockers (ambrisentan, bosentan, macitentan) or prostacyclin derivatives (treprostinil, iloprost and epoprostenol derivatives). Patients who have undergone renal transplantation are on immunosuppressives such as cyclosporine and tacrolimus. Cyclosporine has been found to have a drug-drug interaction with bosentan as well and Ambrisentan leading to dangerously increased plasma concentrations of the drug. It should be expected that, until further data are available, drugs that interact with cyclosporine also interact with tacrolimus; hence clinicians should be aware and monitor closely.

Metastatic pulmonary calcifications
Metastatic pulmonary calcifications are seen in about 60-75% patients with chronic renal disease and are which thought to result due to abnormalities in calcium and phosphate metabolism. Most patients remain asymptomatic, but over time these calcifications may lead to restrictive disease, which may cause intra- and postoperative complications. More importantly they may lead to acute respiratory failure, which has been reported in a small number of cases that may be life threatening. These calcifications show a predominance toward the upper lobes due to a higher blood pH and lower PaCO₂, which leads to an alkaline environment, which is suitable for calcium deposition. CRF patients should be routine screened with chest X-ray and ruled out for any other possible calcium depositing process in the body. Treatment should be initiated prior to transplantation surgery and patient should be monitored with pulmonary function testing.

Lymphoma/Lung cancer
Renal transplant has been recommended as the treatment of choice for end-stage renal disease. It has been shown that transplantation increases the incidence of cancer through multiple mechanisms. In a study by Arichi et al. the cumulative incidences of malignancy increased markedly in the second and third decades after kidney transplantation and these patients with malignancy displayed significantly worse survival than those without cancer. Current guidelines recommend a 2-5 year waiting time for renal transplant candidates that have been successfully treated with cancer. In a study by Kasiske et al., for most common tumors, e.g. colon, lung, prostate, cancer rates were roughly double after kidney transplantation as compared with the general population. Kapoii’s sarcoma, non-Hodgkin’s lymphomas and non-melanoma skin cancers were more than 20-fold increased compared with the general population. All renal transplant candidates should be aggressively monitored and treated for malignancy prior to undergoing surgery.

Conclusion
Renal transplantation remains the gold standard therapy for renal failure. It is thus important to look at the possible pulmonary complications of CRF and renal transplantation. Health care professionals should bear in mind that these conditions and possible risk factors should be addressed prior to surgery. Renal transplant centers should adhere to recommended guidelines of follow a treatment algorithm that addresses the possible pulmonary complications associated with this patient population.

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