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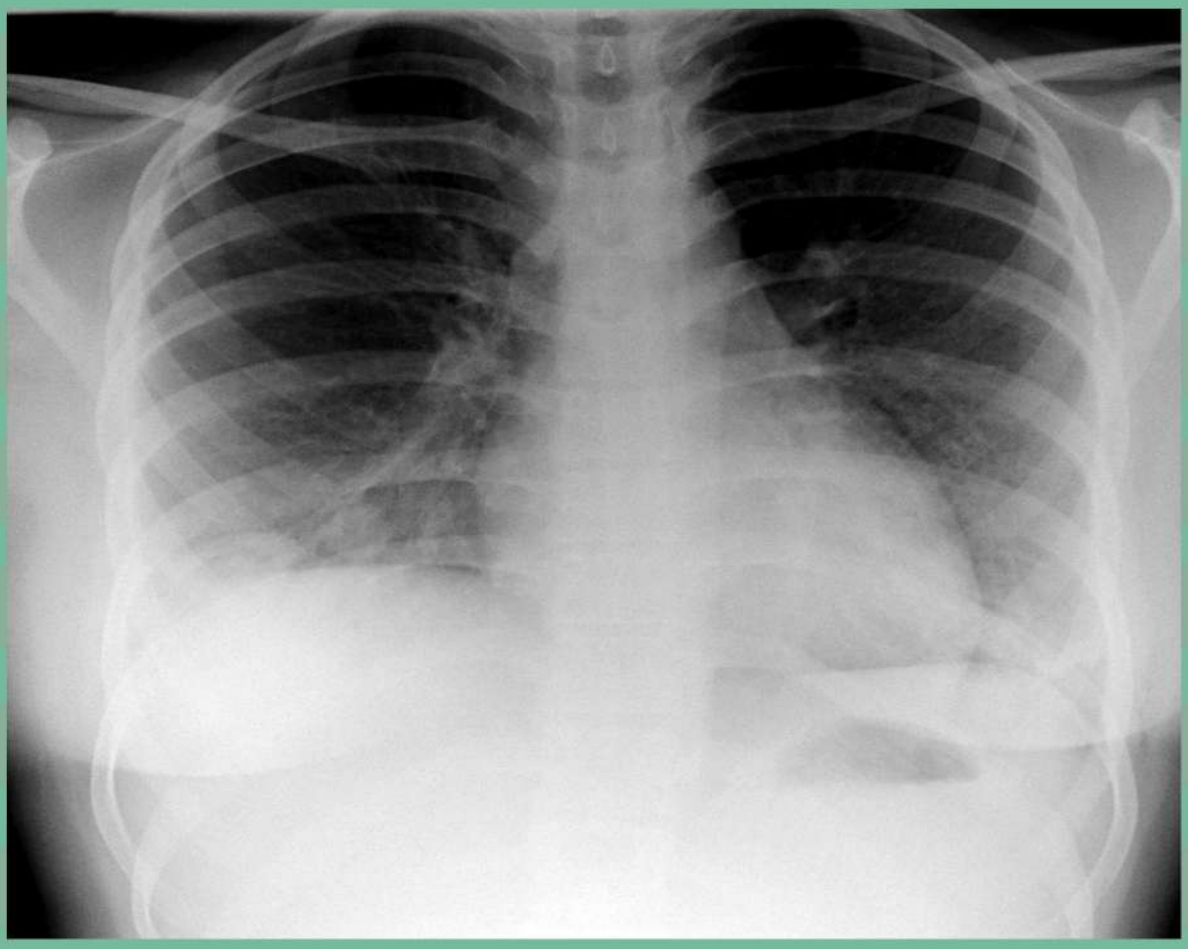

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Editorial

New Ideas on Limitations to $\dot{V}O_{2max}$: Five Major Determinants for $\dot{V}O_{2max}$

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Chronic obstructive pulmonary disease (COPD) is an important and a growing cause of morbidity and mortality worldwide. Cardiovascular, musculoskeletal, metabolic, and mental comorbidities are considered to be part of the frequently prevalent non-pulmonary sequelae of the disease.[1,2] Increasing evidence suggests that extra-pulmonary effects of COPD and airflow limitation are only poorly correlated.[3] Waschki, et al. found that objectively measured physical activity is the strongest predictor of all-cause mortality in patients with COPD.[4]

The association between physical inactivity and poor outcomes are well established for patients with pulmonary disease, cardiac disease, chronic kidney disease.[4-6] Patients with pulmonary disease, cardiac disease, or renal disease typically engage in a lower level of physical activity than do the general population, which can induce a catabolic state including reduced neuromuscular functioning, reduced exercise tolerance and reduced cardiorespiratory fitness (CRF).

CRF is an important consideration, in addition to physical activity, as it is a strong predictor of mortality; low CRF presents a particularly high risk of death compared to other common risk factors, such as diabetes, high cholesterol or hypertension.[7] CR fitness is defined as the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity and is usually expressed as maximal oxygen uptake ($\dot{V}O_{2max}$) during maximal exercise testing.[8] In 2016, the American Heart Association published a scientific statement[9] recommending that CRF, quantifiable as $\dot{V}O_{2max}$, be regularly assessed and utilized as a clinical vital sign. This statement was based on mounting evidence that lower CRF levels are associated with high risk of cardiovascular disease, all-cause mortality, and mortality rates stemming from various types of cancers.

$\dot{V}O_{2max}$ is expressed either as an absolute rate in (for example) liters of oxygen per minute (L/min) or as a relative rate in (for example) milliliters of oxygen per kilogram of body mass per minute (e.g., mL/(kg•min)). The latter expression is often used to compare the performance of endurance athletes and patients.

Figure shows gas transport mechanisms for coupling cellular (internal) to pulmonary (external) respiration. The gears represent the functional interdependence of the physiological components of the system. Cardiac output, pulmonary diffusion capacity, oxygen carrying capacity, renal function and other peripheral limitations like muscle diffusion capacity, mitochondrial enzymes, and capillary density are all examples of $\dot{V}O_{2max}$ determinants.

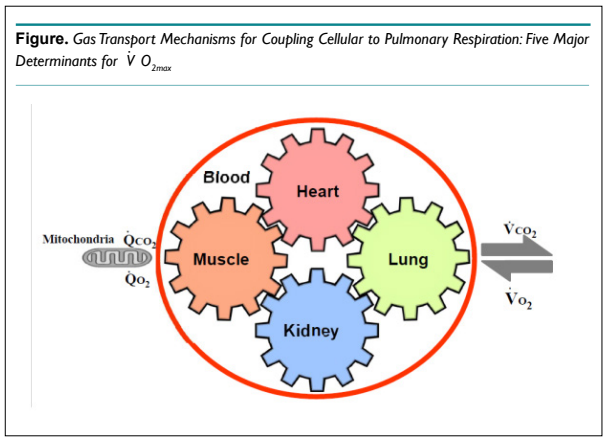

Figure. *Gas Transport Mechanisms for Coupling Cellular to Pulmonary Respiration: Five Major Determinants for* $\dot{V}O_{2max}$

The large increase in O_2 utilization by the muscles (QO_2) is achieved by increased extraction of O_2 from the blood perfusing the muscles, the dilatation of selected peripheral vascular beds, an increase in cardiac output (stroke volume and heart rate), an in-

crease in pulmonary blood flow by recruitment and vasodilatation of pulmonary blood vessels, and finally, an increase in ventilation. O_2 is taken up ($\dot{V}O_2$) from the alveoli in proportion to the pulmonary blood flow and degree of O_2 desaturation of hemoglobin in the pulmonary capillary blood. Metabolic acidosis in chronic kidney disease (CKD) patients promote muscle protein wasting and protein-energy wasting (PEW) by increasing protein degradation[10] and reducing protein synthesis.[11] As a result, maintenance of muscle mass is impaired in CKD patients with altered protein turnover rates.[12] Adding to sarcopenia, metabolic acidosis, protein-energy wasting, angiotensin II, myostatin overexpression in uremia contribute the etiology for muscle wasting in CKD.[13] Moreover, the drug erythropoietin (EPO) can boost $\dot{V}O_{2max}$ by a significant amount in both humans and other mammals.[14]

COPD often coexists with other diseases (comorbidities such as heart disease, CKD, osteoporosis) that may have a significant impact on prognosis. Thirty-three percent of elderly patients with heart failure had COPD and 25% of elderly patients with COPD also had heart failure.[15] This risk of comorbid disease can be increased by the sequelae of COPD; e.g., reduced physical activity. As super-aged society has come, the number of persons with multimorbidity and multiple disabilities (MMD)[16] and their needs of rehabilitation have increased rapidly more than we have expected.[16] $\dot{V}O_{2max}$ offers the investigator the unique opportunity to study simultaneously the cellular, cardiovascular, ventilatory and metabolic systems' responses under conditions of precisely controlled stress. This is of significant practical importance because $\dot{V}O_{2max}$ measured by cardiopulmonary exercise testing, provides what is probably the most sensitive assessment of the effect of new therapy on function of any diseased organ system whose major function is to couple pulmonary gas exchange to cellular respiration. For example, it is important to determine whether new medical, surgical, and rehabilitative procedures can effectively intervene to improve the gas transport capability of a diseased organ system.

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Case Report

A Rare Case of Gemcitabine-Induced Pulmonary Hypertension

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ABSTRACT

Context
Gemcitabine is the backbone of systemic treatment of locally advanced and metastatic intrahepatic cholangiocarcinoma. In recent literature, gemcitabine has been linked to various pulmonary side effects.

Case Report
We report a case of an 82-year-old male who developed acute pulmonary hypertension after receiving one cycle of gemcitabine for metastatic cholangiocarcinoma. His symptoms began with fatigue associated with shortness of breath and cough that worsened despite dose reduction. He developed new onset bilateral pulmonary effusions and an echocardiogram revealed findings consistent with pulmonary hypertension. A computed tomography (CT) angiogram was negative for pulmonary thromboembolism. Although he was promptly treated with diuretics and steroids, the patient could not tolerate any further therapy.

Conclusion
Gemcitabine-induced pulmonary hypertension is rare and can be challenging to diagnose, as it remains a diagnosis of exclusion. However, physicians should be vigilant of new pulmonary symptoms, as delayed treatment can cause significant patient morbidity and mortality.

Keywords
Cholangiocarcinoma; Gemcitabine; Pulmonary hypertension.

Abbreviations
CT: Computed Tomography; PE: Pulmonary Thromboembolism; GIPT: Gemcitabine-Induced Pulmonary Toxicity.

INTRODUCTION

Intrahepatic cholangiocarcinoma is a rare yet aggressive cancer of the biliary tract that portends a poor prognosis.[1] A majority of patients are diagnosed when their disease has already reached a non-resectable, advanced state with a five-year survival of only 30%.[2] Systemic therapy with gemcitabine is often used as either a single agent or in combination with other chemotherapy drugs for both locally advanced and metastatic disease. Gemcitabine is generally well-tolerated, and its most common adverse effects are myelosuppression and gastrointestinal toxicities. In recent literature, gemcitabine has been linked to a variety of severe pulmonary side effects. Despite its low incidence, the spectrum of pulmonary injury is wide, including potentially fatal conditions.[3] We report a case of acute pulmonary hypertension in a patient treated with gemcitabine for metastatic intrahepatic cholangiocarcinoma.

CASE REPORT

An 82-year-old man was brought to the hospital after sustaining a mechanical fall at home and was found to have a non-operable left greater trochanter fracture. On abdominal imaging, he was incidentally found to have a 9.2 cm dominant mass at the dome of the liver straddling the left and right hepatic lobes with a 6 mm

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right lower lobe pulmonary nodule, which was suspicious for metastatic intrahepatic cholangiocarcinoma. A subsequent liver biopsy confirmed moderately differentiated adenocarcinoma. Based on his age and performance status, the patient began treatment with single agent gemcitabine 1000 mg/m² on days one and eight every three weeks in conjunction with pegfilgrastim.

On the fourth day of his first cycle with gemcitabine, the patient developed a blanchable maculopapular rash on his upper chest, which eventually resolved with loratadine and diphenhydramine. However, the patient became increasingly fatigued after day eight of gemcitabine. Due to these side effects, gemcitabine was dose reduced to 500 mg/m² every other week. Although his fatigue improved on the days he did not receive chemotherapy, the patient complained of new onset of shortness of breath and a dry cough that persisted into his second treatment cycle. During an office visit, a pulse oximetry measurement registered the patient as breathing 92% on ambient air. A chest X-ray showed bilateral pleural effusions (Figure 1). Even after initiating furosemide to facilitate diuresis and a short course of corticosteroids, the patient continued to have dyspnea on exertion. The patient, who had no significant history of cardiac or pulmonary disease, underwent a transthoracic echocardiogram, which revealed an estimated pulmonary artery systolic pressure of 35 mmHg assuming a right atrial pressure of 15 mmHg; this finding was consistent with pulmonary hypertension likely secondary to gemcitabine (Figure 2). Computed tomography (CT) angiogram of the chest was performed to rule out pulmonary thromboembolism (PE), and it was negative. The patient was promptly treated with diuretics and gemcitabine was discontinued given the high suspicion of drug related toxicity causing pulmonary hypertension.

Figure 1. *Development of a Right Pleural Effusion after Gemcitabine Treatment*

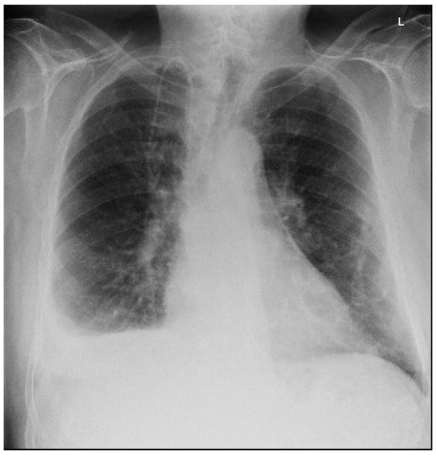
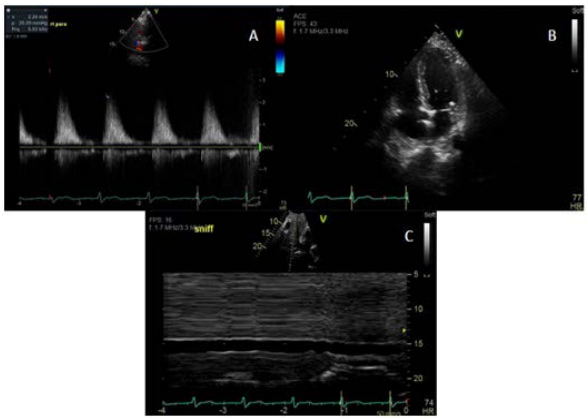


Figure 2. *Images A-C Showing Echocardiographic Evidence of Pulmonary Hypertension*



The patient could not tolerate any further treatment with gemcitabine at which point his regimen was changed to fluorouracil and leucovorin. Despite this, he endured worsening symptoms and ultimately opted for hospice care.

DISCUSSION

Gemcitabine is a pyrimidine analog that is used to treat several malignancies including biliary tract cancers, pancreatic cancer, non-small cell lung cancer, and breast cancer.[4] Although it is relatively well tolerated despite its tendency to be myelosuppressive, gemcitabine-induced pulmonary toxicity (GIPT) is a rare yet critical entity whose incidence remains unknown. Various types of lung injuries have been reported with gemcitabine use including interstitial pneumonitis, diffuse alveolar damage, pulmonary fibrosis, and acute respiratory distress syndrome.[5,6]

While the exact mechanism is unknown, several hypotheses have been proposed to explain the pathogenesis of GIPT. For example, the induction of pro-inflammatory cytokines and an enhanced expression of growth factors are linked to idiopathic pulmonary fibrosis related to gemcitabine use. Furthermore, causative mechanisms including damage to alveoli, pulmonary vasculature, and/or the interstitium may also explain the development of pulmonary hypertension in these patients. In one animal study performed to assess acute and delayed toxicities of gemcitabine, it was found that the drug induces vasoconstriction of the pulmonary capillaries, causing increased mean left main pulmonary arterial pressure.[7]

Pulmonary hypertension, diagnosed through right heart catheterization, is defined by a mean pulmonary artery pressure ≥25 mmHg at rest.[8] In our case, the patient was found to have a pulmonary artery pressure of 35 mmHg. Therefore, right heart catheterization was not performed because clinical suspicion was high enough to start treatment quickly based on the patient's symptoms and diagnostic transthoracic echocardiogram findings in the absence of PE. Despite rapid initiation of treatment with diuretics and steroids, he still only had a suboptimal response likely due to coexisting pulmonary conditions, such as worsening metastatic nodules and malignant pulmonary effusion, which developed later in his disease course.

The time frame from gemcitabine initiation to development of pulmonary toxicity widely varies from as early as 3-days to as late as one year.[5] This makes it challenging for physicians to diagnose GIPT and begin treatment especially when the exact

underlying mechanism remains unknown. Treatment options also vary depending upon the type of lung toxicity. Multiple etiologies such as pulmonary vaso-occlusion, capillary leak, and cytokine-mediated direct toxicity can all contribute to gemcitabine-induced pulmonary hypertension.[5,9] For GIPT, conventional modalities such as diuretics and steroids have been used, however, their benefit in pulmonary hypertension is questionable.[4,10,11] Typically, drug-related pulmonary arterial hypertension is treated with prostacyclin analogues and calcium channel blockers, however, further studies are needed to assess their efficacy in cases associated with gemcitabine. Perhaps anti-cytokine agents could also be implemented to reduce the cytokine burden incited by gemcitabine.

CONCLUSION

Gemcitabine-induced pulmonary hypertension and other lung toxicities remain a diagnosis of exclusion. However, physicians should remain vigilant of detecting and treating symptoms when they arise. Untreated pulmonary hypertension can cause significant morbidity and mortality, and therefore, early recognition of this condition is essential. Further development of new treatment modalities, based on the suspected mechanisms, is needed to ensure good patient outcomes.

CONSENT

The authors have received written informed consent from the patient.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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