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Pancreatic cystosis in cystic fibrosis: Sometimes a bike ride can help you decide

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ABSTRACT

Pancreatic cystosis (PC) is an uncommon manifestation of pancreas involvement in cystic fibrosis (CF), characterized by the presence of multiple macrocysts partially or completely replacing pancreas. Only few reports are available from literature and management (surgery vs follow up) is commonly based on the presence of symptoms or complications due to local mass effect, although evidence-based recommendations are still not available.

We here report the case of a young adult CF patient with PC, in which cardiopulmonary exercise testing (CPET) provided important information to be integrated to the radiological finding of inferior vena cava compression by the multicystic pancreas complex. Through the analysis of oxygen kinetic cardiodynamic phase pattern, CPET may be helpful to safely exclude significant mass effects on blood venous return and to improve the decision-making process on whether to consider surgery or not in patients with PC.

1. Introduction

Cystic fibrosis (CF) is the most common lethal autosomal recessive genetic disorder among Caucasians, with highest prevalence in Europe, North America and Australia, occurring in approximately 1 in 2500 live-births [1]. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) are responsible for the pathogenesis of the disease.

CF is a multi-system disease classically involving upper and lower airways, pancreas, liver and the reproductive tract. Typically, pancreatic involvement results in partial or complete replacement by fibro-fatty tissue, diffuse pancreatic fibrosis, pancreas atrophy and multiple cysts. Whilst small pancreatic cysts are relatively common, the finding of multiple macrocysts (i.e. > 1 cm in size) replacing pancreas is a rare complication of CF and is referred to as pancreatic cystosis (PC) [2].

Pathophysiology of PC is postulated to be related to the intra-ductal defective bicarbonate secretion secondary to the CFTR channel dysfunction, leading to inspissated secretions, increased pressure within pancreatic ducts and transformation into various-sized cysts [3].

Most patients are asymptomatic, with radiographic findings discovered incidentally on ultrasound or magnetic resonance imaging (MRI), usually during the second decade of life [4]. When present, symptoms occur secondary to mass-effect, vascular compromise and/or intra-cystic

hemorrhage. Management is based purely on symptoms and/or complications, with no influence exerted by cyst size. If symptoms warrant intervention, either pancreatectomy or endoscopic cystogastrostomy are the only available surgical options [2].

We here report a case of PC in which cardiopulmonary exercise testing (CPET) helped define the functional consequences of compression of the inferior vena cava (IVC) found at imaging.

1.1. Oxygen kinetics to assess venous return: rationale

In a given individual, the profile of oxygen consumption ($\dot{V}O_2$) by peripheral muscles and lungs following the onset of constant-work rate exercise may be defined with respect to the exercise intensity domain in which the exercise itself is performed which, in turn, is determined by clusters of common metabolic responses evoked.

Specifically, as shown in Fig. 1, for moderate intensity exercise (i.e. before the onset of a substantial anaerobic metabolism, so called lactate threshold, θ_L), $\dot{V}O_2$ measured at the lungs follows a three-phase kinetic [5]. Phase I (also called cardiodynamic component) is usually characterized by an immediate increase in oxygen uptake at the start of exercise, lasting for 15–20 seconds. It is accounted for by the abrupt rise in pulmonary blood flow secondary to an almost immediate increase in

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heart rate, stroke volume and, therefore, cardiac output, facilitated principally by the instantaneous vagal withdrawal and the mechanical pumping action of the contracting muscles. Phase II (primary component) is defined by the exponential growth in $\dot{V}O_2$ values reflecting the period of major increase in cellular respiration and lasting approximately 3–4 minutes, until the achievement of a steady state for $\dot{V}O_2$ (phase III) [5,6].

Phase I is believed to be driven by the increase in pulmonary blood flow in the absence of altered arterial or venous O_2 contents [6,7]. Indeed, lung $\dot{V}O_2$ is the product of cardiac output times the arterial-venous O_2 content difference. The exponential increase in muscle O_2 uptake at exercise onset and the sequelae for muscle-venous and mixed-venous blood composition are not immediately expressed at the lungs, being delayed by the so-called muscle-to-lung transit delay. As the arterial-venous O_2 content difference is effectively unchanged from rest over this interval, the increase in pulmonary $\dot{V}O_2$ is determined by cardiac output only or, strictly speaking, pulmonary blood flow which is a direct consequence of an equal increase in venous return to the right atrium [7].

2. Case presentation

A 24-year-old male affected by CF came to our attention looking for a second opinion about surgical indication due to PC determining compression on IVC. CF diagnosis was made through newborn screening and subsequent CFTR genotyping revealed homozygosis for F508del mutation. CF-related complications included chronic airways infection by *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Stenotrophomonas maltophilia*, exocrine pancreatic insufficiency, chronic rhinosinusitis, cholelithiasis and nephrolithiasis. Other non-CF comorbidities included β thalassemia minor and hypersensitivity to *Dermatophagoides pteronyssinus*. At the time of evaluation, he still had a preserved lung function (forced expiratory volume in the 1st second, FEV₁: 3.73 L, 87% predicted value; forced vital capacity, FVC: 4.64 L, 92% predicted value) as well as a good nutritional status (body mass index: 21.7 kg/m²).

PC was first found incidentally seven years before, during routine abdominal ultrasound. Since then, patient performed regular follow up with ultrasound (annually) and RMI (biannually), showing very slow but progressive growth of multiple cysts mainly involving the head and the

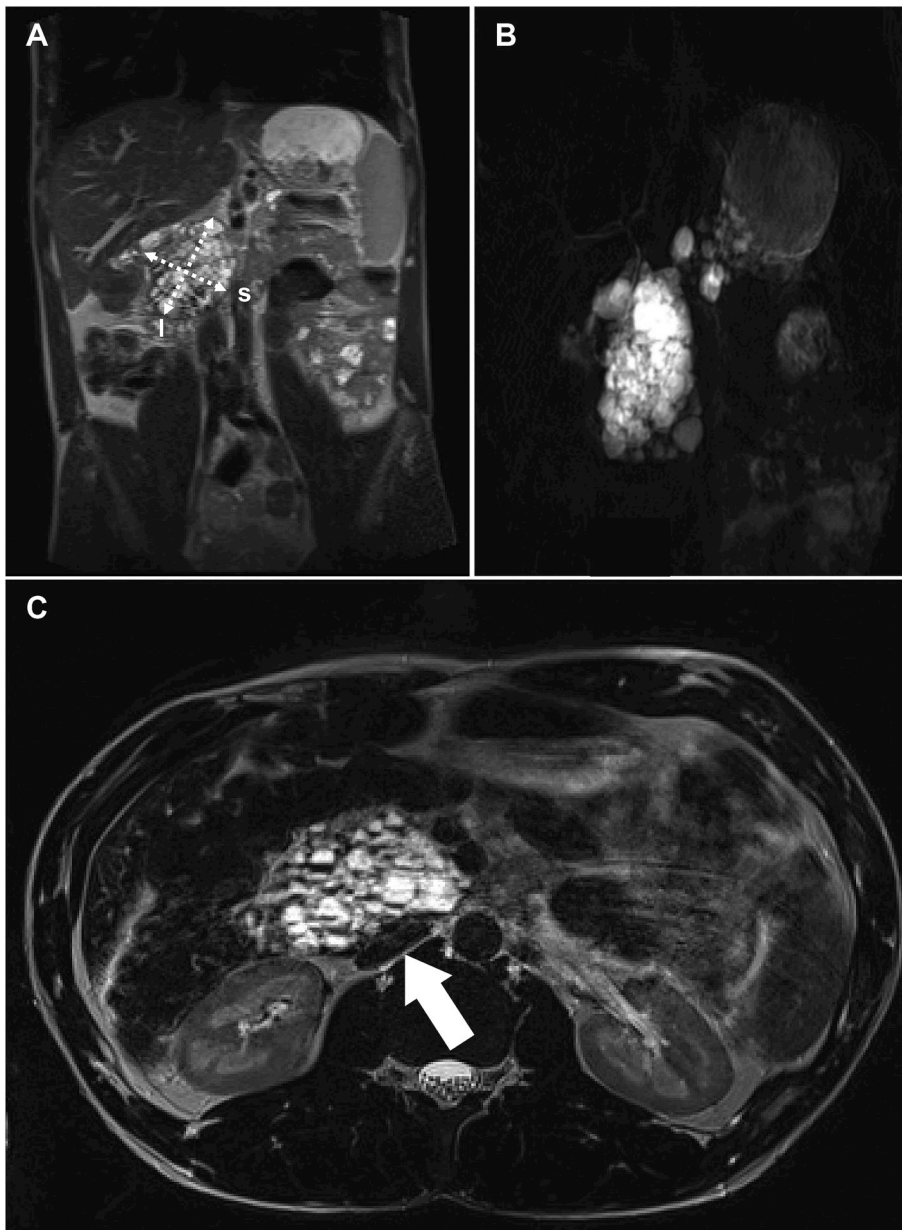


Fig. 1. Abdominal MRI showing multicystic transformation of the entire pancreas consistent with the diagnosis of pancreatic cystosis. A) T2-weighted Half fourier Single-shot Turbo spin-Echo (HASTE) sequence coronal section showing the multicystic complex long- (l) and short-axis (s) diameters, measuring 87.4 mm and 68.6 mm, respectively; B) T2-weighted coronal volumetric reconstruction of biliary tree showing the well-defined hyperintense multicystic complex; C) Fat saturated T2-weighted sequence axial section showing the compression of the subrenal trait of the inferior vena cava anterior wall (white arrow) by the cystic complex (see main text for further details).

uncinate process of the pancreas. Patient denied symptoms such as abdominal pain, nausea, fullness as well as episodes of mechanical intestinal occlusion. A palpable, painless mass in mesogastrium, with no defined limits, was appreciable at physical examination. No evidence of jaundice, peripheral edema and collateral venous circulation was found.

Abdominal MRI was repeated (Fig. 2), which showed multicystic transformation of the entire pancreas with no residual normal parenchymal tissue and no pancreatic duct dilation. The whole multicystic complex measured $69 \times 60 \times 87$ mm, apparently unchanged over the last two years, determining a mild widening of the duodenal C-loop. The largest cyst's diameter measured 2 cm. Bile ducts were poorly appreciable due to massive local anatomical changes. Infusion of gadolinium contrast medium confirmed the compression of the subrenal trait of the IVC against lumbar backbone. Finding of two subcentrimetric gallstones was confirmed as well. Liver, spleen, kidneys and adrenal glands were apparently unaffected.

2.1. Patient's oxygen kinetics

Incremental symptom-limited CPET was first performed on an electronically braked cycle ergometer through automated testing system (OMNIA, Cosmed, Rome, Italy) to identify θ_L . The test was performed with a 10 W/min incremental work rate protocol until physical exhaustion. θ_L occurred at work rate of 70 W, corresponding to a $\dot{V}O_2$ value of 16.9 ml/min/kg (36.7% of maximal $\dot{V}O_2$ predicted). A tailored constant work rate CPET was then performed 24 hours later at a moderate exercise intensity (i.e. below θ_L) of 50 W. No warm-up was performed to avoid misinterpretation of oxygen kinetics phase I.

As shown in Fig. 3, the three phases of oxygen kinetics were clearly discernible: after ≈ 20 sec of rapid increase in $\dot{V}O_2$ values (phase I), exponential rise in $\dot{V}O_2$ (phase II) was observed and steady state (phase III) was finally reached after ≈ 4 min from the beginning of exercise. $\dot{V}O_2$ averaged value at rest was 491.4 ml/min, while at steady state was 1375 ml/min. Hence, rest-to-steady state rise in $\dot{V}O_2$ ($\Delta\dot{V}O_2$) was 883.6 ml/min, with approximately 441.6 ml/min increase recorded during phase I only (+89.9% from baseline, 49.9% of $\Delta\dot{V}O_2$).

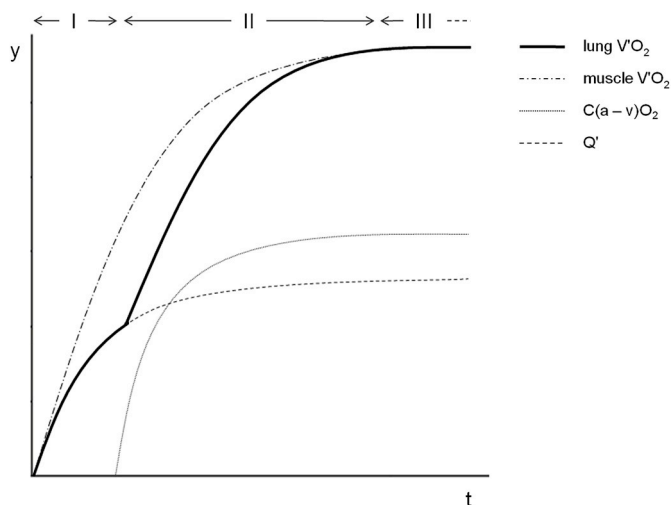


Fig. 2. Schematic representation of physiologic responses to constant-work rate exercise below lactate threshold. The three phases (I, II, III) of oxygen uptake ($\dot{V}O_2$) kinetics are shown. Note that for the great majority of phases I and II muscle $\dot{V}O_2$ is not immediately expressed at the lungs, being delayed by the muscle-to-lung transit delay. Indeed, during phase I, changes in $\dot{V}O_2$ measured at the lungs are secondary to the increase in cardiac output (Q'), whilst modifications in arterial-venous oxygen content ($C(a-v)O_2$) begins and are accounted for only after some time from the beginning of physical effort (i.e. end of phase I). See main text for further explanations.

3. Discussion

PC is a rare complication of CF with an unknown prevalence due to the paucity of information available from literature, mostly represented by case series [8–18]. A recent systematic review on this topic was published by Desai CS et al. [4], who identified 19 papers describing a total of 24 cases only of PC since 1981. Despite the lack of proper evidence-based recommendations, there is common agreement that the clinical management of PC should be driven by symptoms and/or abdominal complications secondary to cysts mass-effect or hemorrhage [2].

As for our patient, the great majority of reported cases are characterized by asymptomatic individuals with incidental finding of PC who were suggested to continue with radiological follow up. Surgery has been described in few cases only for symptomatic patients, with interventions going from endoscopic cystogastrostomy to laparotomy with partial to total pancreatectomy [4,16,17], the latter recently described in association with islet cell autotransplantation [8]. In all these cases, no mention was done of compression on major abdominal vessels and hemodynamic consequences arising from PC. To our knowledge, this is the first case described of PC where decision making, i.e. whether undergoing surgery or not, was specifically focused on the presence of functional effects stemming from IVC mechanical compression.

In this situation, CPET may represent a helpful diagnostic tool, allowing non-invasive assessment of venous return through the analysis of oxygen kinetics during constant-work rate exercise at a moderate intensity (i.e. below θ_L). The point has been made clear previously that, in this condition, the rapid increase in $\dot{V}O_2$ values during phase I represents an indirect index of the lack of abnormalities in right heart cardiac output which, in subjects with no evidence of increased pulmonary blood pressure, is directly related to venous return.

Though, it must be clarified that no reference values are available to define a normal/abnormal response, specifically with regard to the magnitude of $\dot{V}O_2$ response during phase I [19]. Nonetheless, previous studies observed that among healthy individuals, at the end of phase I, $\dot{V}O_2$ approximately doubles its resting value [6,20], corresponding to approximately $50 \pm 11\%$ of rest-to-steady state change in $\dot{V}O_2$ [21]. These values are significantly reduced among patients affected by cardiovascular diseases with increased right heart pressures, such as chronic heart failure and cyanotic congenital heart diseases. In our case, we observed a change in $\dot{V}O_2$ which almost doubled its resting value (+89.9% from baseline) and corresponded to half the change in $\dot{V}O_2$ during the exercise testing, which is comparable to the response typically observed in healthy individuals. Answering the patient's clinical question, we non-invasively excluded functional abnormalities arising from IVC compression by multiple pancreatic cysts and confirmed the absence of any clear indication to surgery; he was therefore suggested to continue with regular follow up through ultrasound and MRI.

4. Conclusion

PC is a rare complication of CF, with still little information available on proper management. Surgery is indicated for patients with abdominal symptoms and complications manifestly related to mass-effect. Although, functional complications secondary to compression *ab extrinseco* on main abdominal vessels may be difficult to assess. Referral to a highly specialized center in exercise physiology and evaluation of the cardiodynamic component of oxygen kinetics during CPET may add valuable information for the management of these cases.

Consent for publication

Written informed consent was obtained from the patient for anonymous publication of this case report. A copy of written consent is available upon request.

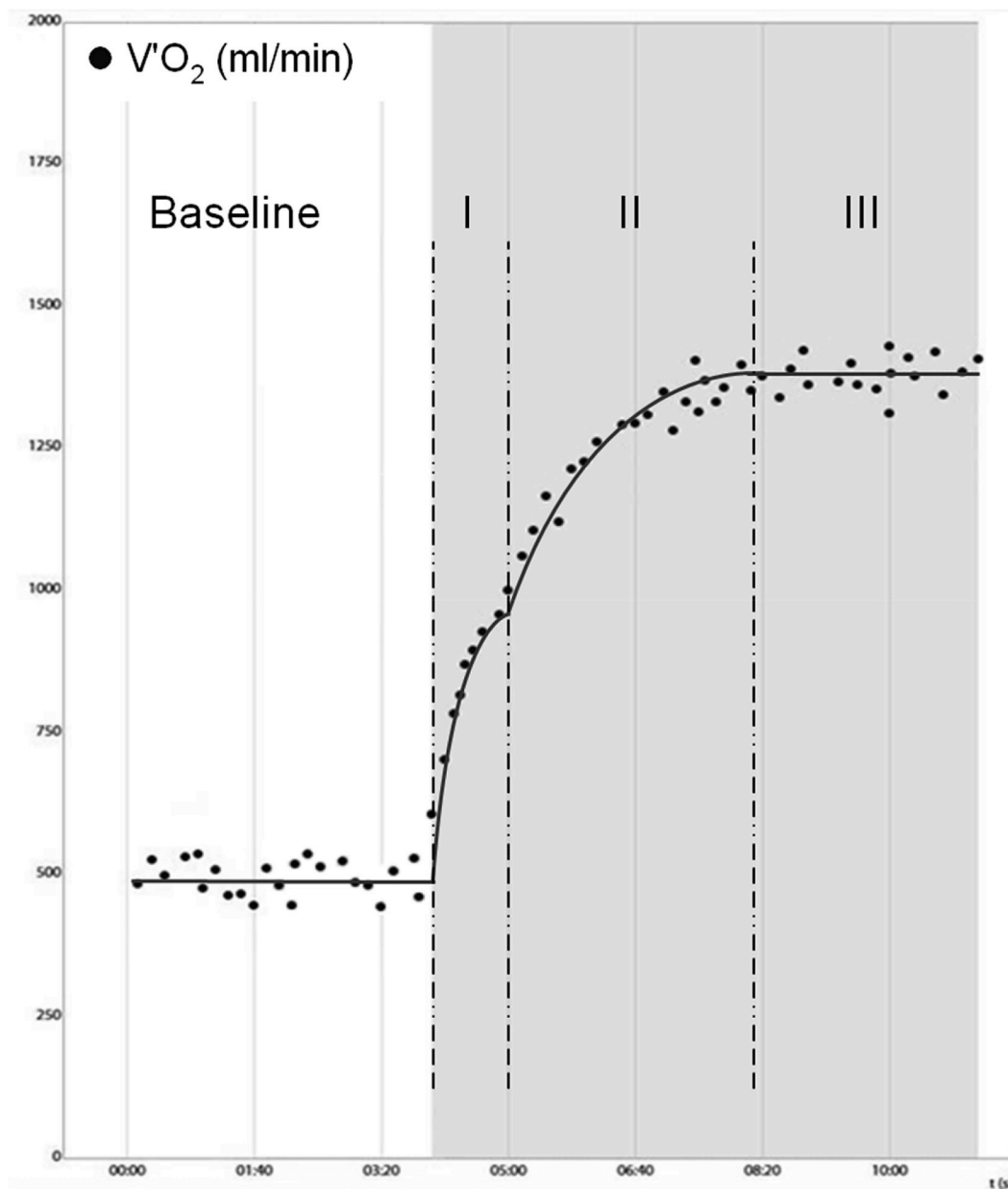


Fig. 3. Patient's oxygen kinetics in response to cardiopulmonary exercise testing at 50 W (below lactate threshold). Shaded area represents exercise. Oxygen uptake ($\dot{V}O_2$) is shown in its typical three-phase behavior. Increase in $\dot{V}O_2$ observed during phase I corresponded approximately to 50% of the whole rest-to-steady state change (almost double the baseline value).

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Authors' contributions

MDP: conception and design of paper, execution of cardiopulmonary exercise testing, acquisition and interpretation of data, review of literature, writing and revision of manuscript, processing of figures, approval of final version; ADG: execution and interpretation of magnetic resonance imaging, processing of figures, approval of final version; ELI: execution and interpretation of magnetic resonance imaging, processing of figures, approval of final version; MM: execution of cardiopulmonary exercise testing, review of literature, approval of final version; PP: conception and design of paper, approval of final version.

Declaration of competing interest

Declarations of interest from authors: none.

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