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CLINICAL TRIALS STUDY

Chronic permanent hypoxemia predisposes to mild elevation of liver stiffness

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Abstract

AIM: To evaluate the impact of long term permanent hypoxemia noticed in patients with non operated congenital cyanogenic cyanotic cardiopathy on liver stiffness.

METHODS: We included ten adult patients with non operated inoperate cyanotic cardiopathy and ten matched patients for age and gender admitted to the gastroenterology department for proctologic diseases; Clinical and laboratory data were collected [age, gender, body mass index, oxygen saturation, glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), glycemia and cholesterol]. Measurement of hepatic stiffness by transient elastography was carried out in all patients using the Fibroscan device. All patients underwent an echocardiography to eliminate congestive heart failure.

RESULTS: Among the patients with cyanotic cardiopathy, median liver stiffness 5.9 ± 1.3 kPa was greater than control group (4.7 ± 0.4 kPa) (P = 0.008). Median levels of GOT, GPT, gamma-glutamyltransferase, glycemia and cholesterol were comparable in cardiopathy and control group. In regression analysis including age, gender, body mass index, oxygen saturation, GOT, GPT, glycemia, cholesterol showed that only oxygen saturation was related to liver stiffness (r = -0.63 P = 0.002).

CONCLUSION: Chronic permanent hypoxemia can induce mild increase of liver stiffness, but further studies are needed to explore the histological aspects of liver injury induced by chronic permanent hypoxemia.

Key words: Liver; Cardiopathy; Hypoxemia; Stiffness; Cyanotic

Core tip: Our study is the first one to be carried out in humans and to evaluate the long term effect of hypoxemia on liver stiffness. The clinical model is provided by non operated adult patients with cyanotic cardiopathy. Heart failure, that can overestimate liver stiffness, is eliminated by echocardiography in all patients. The results show that long term hypoxemia leads to only mild liver stiffness elevation.

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INTRODUCTION

Recent evidence indicates that chronic intermittent hypoxemia (CIH), related to obstructive sleep apnea, is associated with non-alcoholic steatohepatitis (NASH) and chronic liver injury in obese individuals[1-3]. Also, CIH has also been associated with an increased risk of hypertension, type 2 diabetes, dyslipidemia, and atherosclerosis, independently of underlying obesity[4-8]. Moreover, in rodent models, CIH can lead to insulin resistance, dyslipidemia and hypertension. non operated patients with cyanotic cardiopathy provide clinical models of long term exposition to hypoxemia The effect of chronic permanent hypoxemia in cyanotic cardiopathy on liver stiffness, glycemia and triglycerid and cholesterol levels is unknown in humans.It is still unclear if permanent hypoxemia has the same effects on liver, glycemia, triglycerid and cholesterol levels as intermittent chronic hypoxemia does. Furthermore, exposure of primary mouse hepatocytes to permanent 1% oxygen stimulates nuclear accumulation of HIF-1α and upregulated PAI-1, vascular endothelial cell growth factor, and the vasoactive peptides adrenomedullin-1 (ADM-1) and ADM-2[9].

Liver stiffness measurement using Fibroscan is a non-invasive method for diagnosis of liver fibrosis. It also has a high degree of accuracy and reproducibility in predicting bridging fibrosis, cirrhosis and prognosis in patients with chronic liver diseases even in non-alcoholic fatty liver disease (NAFLD)[10-15].

The aim of the study is to assess the impact of chronic permanent hypoxemia noticed in patients with non operated cyanotic heart disease on liver stiffness and metabolic defining criteria (glycemia, cholesterol and triglycerid levels).

MATERIALS AND METHODS

We included all alive adult patients having non operated cyanotic cardiopathy followed in the Cardiology Department of Ibn Rochd Hospital Center and control group matched for age and gender admitted to gastroenterology department for proctologic diseases (anal fissure, hemorrhoids, anal fistula). Clinical and laboratory data were collected [age, gender, body mass index (BMI), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase alanine transaminase (ALT), glycemia, triglycerides and total cholesterol, oxygen saturation, liver stiffness]. Oxygen saturation measurement with pulse oximetry were obtained.

Using a SIEMENS pulse oximeter (Siemens Medical Electronics, Danvers, United States) connected to a re-usable finger sensor probe NELLCORTM DS-100A Durasensor® (Nellcor Puritan Bennett Inc., Pleasanton, United States). The cyanotic cardiopathy was Fallot Tetralogy in 5 cases, pulmonary atresia with intact ventricular septum in 1 case, tricuspid atresia in 1 case, transposition of great vessels in 1 case and double outlet right ventricule (DORV) in 2 cases (Table 1). All patients underwent an echocardiography to exclude out a heart failure that can overestimate liver stiffness. None of the patiens had cardiac failure at the time of the study or as a known medical antecedent.all of the included patients were negative of hepatitis B and C and none of them was alcohol consumer.

Table 1 Caracteristcs of pataients with cyanotic cardiopathy

Patients	Age (yr)	Diagnosis	Oxygen saturation	Liver stiffness (kPa)
1	33	Transposition of the great vessels	80%	7. 2
2	20	Tricuspid atresia, malposition of the great vessels and pulmonary atresia	86%	5.9
3	25	Fallot Tetralogy	87%	6.1
4	22	tricuspid atresia + malposition of the great vessels + interventricular communication	87%	4.0
5	32	Fallot Tetralogy	97%	6.5
6	20	Double outlet right ventricle with severe pulmonary stenosis.	90%	3.7
7	20	Double outlet right ventricle + pulmonary atresia	78%	7.8
8	42	Fallot Tetralogy	76%	6.4
9	24	Fallot Tetralogy	87%	4.8
10	26	Fallot Tetralogy	85%	6.9

Liver stiffness measurement was performed using Fibroscan (Echosens, Paris, France) with the patient lying in dorsal decubitus with the right arm in maximal abduction, on the right lobe of the liver, through intercostals spaces. The operator, assisted by a time-motion ultrasound image, located a liver portion at least 6cm thick and free of large vascular structures. When the target area had been located, the operator pressed the M probe button to launch the measurements. The measurement depth ranged between 25 and 65 mm. Ten validated measurements were performed on each patient. The results were expressed in Kilopascals (kPa). Only procedures with at least 10 validated measurements and an interquartile range (IQR) inferior to 30% of the median value were considered reliable[16,17]. The measurement of liver stiffness was performed in our unit by the same specialized physician[10].

This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Patients were informed about the procedure and asked for informed consent prior to inclusion in the study.

Statistical analysis

Continuous variables are expressed as mean ± SD. The relationship between LS and each variable was assessed using Pearson's correlation coefficient and LS was compared between two groups using the unpaired Student's *t*-test. Categorical data were compared using the χ^2 test. $P < 0.05$ was considered to represent a statistically significant difference. Data were statistically analyzed using SPSS 16 software.

RESULTS

The value of liver stiffness in cyanotiic cardiopathy pa-

Table 2 Characteristics of patients with cyanotic cardiopathy and control

	Patients w cyanotic cardiopathy	Control	*P* value
Case (male/female)	3/7	3/7	
Age (yr)	26.4	27.1	0.540
BMI (kg/m^2)	19.21 ± 4.8	18.64 ± 2.52	0.460
AST (IU)	23.12 ± 7.33	23.75 ± 4.94	0.370
ALT (IU)	23.9 ± 6.93	24.9 ± 5.43	0.080
Cholesterolg (/L)	1.22 ± 0.24	1.25 ± 0.26	0.830
Triglycerideg (/L)	0.85 ± 0.23	0.98 ± 0.18	0.910
Gylcemiag (/L)	0.97 ± 0.09	0.92 ± 0.01	0.830
GGT (IU)	39.9 ± 18.65	41.1 ± 13.39	0.330
Liver stiffness (kPa)	5.93 ± 135	4.74 ± 0.40	0.008
Saturation (%)	85.4 ± 6.1	99.5 ± 0.52	0.005

BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyltransferase.

Table 3 Relationship between liver stiffness and other factors in all participants

	Correlation coefficient (*r*)	*P* value
Glycemia	0.11	0.63
GOT	0.07	0.76
GPT	-0.19	0.39
GGT	0.009	0.97
T. cholesterol	0.17	0.45
Triglyceridemia	-0.21	0.35
Saturation	-0.63	0.002

GOT: Glutamate oxaloacetate transaminase; GPT: Gamma-pyruvate transaminase; GGT: Gamma-glutamyltransferase.

tients (n = 10) was 5.9 ± 1.35 and that in healthy control group matched for age, gender and BMI was 4.7 ± 0.4. The difference between the two groups is significant (P = 0.005).

All other parameters including BMI, cholesterol, triglyceride, glycemia were comparable in the two groups: only oxygen saturation was lower in cyanotic group (85.1 ± 6.1) as compared to healthy control (99.5 ± 0.5) (P = 005). Table 2 shows background of all patients with cyanotic cardiopathy and control.

Liver stiffness significantly correlated with oxygen saturation (r = -0.63, P = 0.002), while it was not correlated to glycemia, total cholesterol, triglyceridemia, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, and GGT (Table 3).

DISCUSSION

The first interesting finding of our study indicates that the long term effect of permanent hypoxemia on the liver stiffness in non obese patient is mild.

Liver fibrosis is initiated when chronic liver injury stimulates numerous cells types, including hepatocytes, bile duct epithelial cells, Kupffer cells and other inflammatory cells to produce mediators (*e.g.*, growth factors, chemokines, reactive oxygen species). These mediators cause cells in the liver, such as hepatic stellate cells, perbiliary fibroblasts, hepatocytes, bile duct epithelial cells, and bone marrow-derived cells to differentiate into myofibroblasts. Additionally, these mediators stimulate myofibroblast proliferation[18] and stimulate these cells to migrate to injured regions of the liver (*i.e.*, chemotaxis)[19,20]. Once the myofibroblats accumulate in these areas, they are stimulated to produce collagen and other components of extracellular matrix causing fibrosis.

Hypoxia has been shown to play a role in liver fibrosis through hypoxia-inducible factors (HIFs). HIFs are a group of transcription factors rapidly activated in hypoxic cells. Active HIF consists of an alpha subunit and beta subunit. Three alpha subunits termed HIF 1 α, HIF 2α and HIF 3α have been described. All bind to a commun β subunit named HIF1 β. Once activated, these transcription factors regulate expression of genes that allow cells to adapt to a hypoxic environment[21,22].

Exposure of primary mouse hepatocytes to permanent hypoxia (1% oxygen) stimulates nuclear accumulation of HIF-1α and upregulates porofibrotic and vasoactive factors as PAI-1, vascular endothelial cell growth factor, and the vasoactive peptides adrenomedullin-1 (ADM-1) and ADM-2. But exposure of HIF-1β-deficient hepatocytes to 1% oxygen completely prevents upregulation of PAI-1, vascular endothelial growth factor (VEGF), and ADM-1[9].

Furthermore, it is proven that permanent hypoxemia can stimulate epithelial to mesenchymal transition of hepatocytes. During the development of liver fibrosis, an important source of myofibroblasts is hepatocytes, which differentiate into myofibroblasts by epithelial to mesenchymal transition. Exposure of hepatocytes to hypoxemia 1% oxygen increased expression of a smooth muscle actin, vimentin, Snail and fibroblast-specific protein-1 (FSP-1). Upregulation of FSP-1 and Snail by hypoxemia is completely prevented in HIF-1 β deficient hepatocytes[23]. However, in studies carried out in rodents, only the effect of intermittent hypoxemia was studied and there are no studies focusing on permanent hypoxemia, such as seen in cyanotic cardiopathy, and studying its effect on the liver.

CIH results in repetitive cycles of hypoxemia and reoxygenation, leading to excessive production of reactive oxygen species and oxidative stress in various organs and tissues[24]. Yet, intermittent hypoxemia causes lipid peroxidation in different organs and is associated with increased serum levels of amalondiadehyde amalondialdehyde (MDA) and 8-isoprostane, which are products of lipid peroxidation.thus, CIH in mice increases MDA and isoprostane levels in the brain as well as activity of NADPH oxidase, an enzyme-producting superoxide dismutase. CIH also increases MDA levels in the myocardium and decreases activity of an important endogenous antioxidant superoxide dismutase.

However, in the liver, intermittent hypoxemia alone seems unable per se to induce liver fibrosis. In Takatama study. Choline-deficient high-fat diet (CDHF) associated with intermittent hypoxemia for 4 wk is confirmed to induce histological changes that resemble those NASH, associated to biochemical liver dysfunction, while intermittent hypoxemia group liver is normal[25]. Also, CIH in lean C57BL/6J mice causes an increase in serum ALT, while AST and alkaline phosphatase are unchanged. Liver histology shows no evidence of hepatic steatosis or fibrosis, but reveals swelling of hepatocytes, and marked accumulation of glycogen in hepatocytes[26]. Moreover, Increased MDA/free fatty acids (FFA) levels and active nuclear factor kappa B (NF-κB) in the nuclear fraction of hepatocytes are observed in CIH mice as compared to control animals suggesting that CIH induces oxidative stress in the liver. In the absence of obesity, CIH leads to mild liver injury *via* oxidative stress and excessive glycogen accumulation in hepatocytes, while fibrosis is not developed.

Patients with congenital heart disease through chronic hypoxemia and ischemia reperfusion episodes are also exposed to excessive oxygen radicals, total oxidant status; oxidative stress index is higher in the cyanotic patients than in the acyanotic group and controls[27]. Furthermore, it has been proven that the increase of free oxygen radicals, which depends on the degree of chronic hypoxemia in cyanotic congenital heart disease, lay the foundations for several diseases such as atherosclerosis[28]. Free oxygen radicals play an important role in tissue damage with inadequate blood circulation.

In our study, we observed for the first time in humans, that chronic permanent hypoxemia is only associated with mild elevation of stiffness but it is unclear if its due to glycogenic hepatopathy or mild liver fibrosis. The second major finding in our study is the non supervention of glycemia, triglycerid and cholesterol levels elevation in chronic hypoxemic patients with non operated cyanotic heart disease.

Studies in rodent models of intermittent hypoxia demonstrated that CIH can cause insulin resistance, and dyslipidemia[26,29-32]. Furthermore, several crossectional studies suggest that CIH seen in OSA is independently associated with increased levels of total cholesterol, LDL and triglycerides, whereas others report no such relationships[7,33-35]. Many studies show that OSA treatment with continuous positive airway pressure (CPAP) may have a beneficial effect on lipid profile[8,36]. CIH was also proven to be associated with increased prevalence of type 2 diabetes[37] and has recently been shown to be a risk factor for diabetes incidence[38]. In non-diabetics, CIH is associated with insulin resistance in proportion to the degree of nocturnal hypoxemia[39-41].

CPAP can reverse the insulin resistance of OSA both acutely (within 2 d) and chronically (after 4 mo)[42]. Recently, healthy human volunteers have been exposed to hypoxemia by inspiring hypoxic N_2-O_2 gas mixture until the oxyhemoglobin saturation dropped to 85%. After 5H, an intravenous glucose tolerance test demonstrated a decrease in both insulin sensitivity and glucose effectiveness by minimal modeling methods[43]. Interestingly, Chronic permanent hypoxemia, such as described in our clinical model seems not to induce neither hyperglycemia, nor hypercholesterolemia, nor hypertriglyceridemia.

Our study has many advantages. Firstly, it is the first study carried out in humans concerning the effect of long term hypoxemia on the liver provided by non operated patients with cyanotic cardiopathy.secondly, our study shows that long term effect of chronic hypoxemia did not induce neither hypeglycemia nor dyslipidemia. On other hand, our sudy has several limitations. The first is absence of liver biopsy that can be done because of ethic restrictions. The second is the small number of patients included in our study due to the rareness of adult alive patients with cyanotic cardiopathy.

Permanent hypoxemia found in non operated patients having cyanotic cardiopathy leads to mild elevation of liver stiffness, further studies using liver biopsies are needed to explore the nature of the liver damage observed in long term hypoxemic patients.

COMMENTS

Background

Recent evidence indicates that chronic hypoxemia is associated with angiogenesis and liver injury. This clinical evidence comes mostly from case-series of patients with metabolic syndrome and sleep apnea syndrome. However, it is still unclear if long term hypoxemia *per se*, without a metabolic syndrome, can induce liver injury or not.

Research frontiers

Hypoxemia was suspected to be major stimulus for hepatic angiogenesis and fibrogenesis. Anti-angiogenic molecules can be a therapeutic alternative to prevent liver fibrosis progression.

Innovations and breakthroughs

This study was carried out in a clinical model of long term hypoxemia. This sample was provided by adult patient with non operated cyanotic cardiopathy. Heart failure, that can overestimate liver stiffness, was excluded in all patients. This study is interesting because all the patient do not have metabolic syndrome; consequently, the isolate effect of long term hypoxemia is independently measured.

Applications

This study proves that long term hypoxemia in patient without metabolic syndrome induces mild liver elevation of liver stiffness.

Terminology

Cyanotic cardiopathy: is a group type of congenital heart defects. The patient appear blue due to desoxygenated blood bypassing the lungs and entery the systemic circulation

Peer review

This is an interesting study including a small sample size population of patients with cyanotic congenital cardiac disease and a well matched control group, the conclusion of the study is that patients with hypoxemia associated to heart disease showed a higher fibrosis score as compared with the control group. This study is original and the hypothesis is clearly formulated.

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