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Research Article

Use of "LIMON Test" in Constrictive Pericarditis: A Preliminary Case Series

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Abstract

Background: Constrictive pericarditis causes progressively impaired diastolic filling of the heart with associated symptoms of congestive heart failure. High filling pressure in the right atrium creates high hepatic venous pressure with subsequent impairment liver function. Hepatic function has been proposed as an indirect index of cardiac failure in constrictive pericarditis. A non-invasive liver function monitoring system, "LIMON Test", has been developed to measure indocyanine green elimination (ICG) by pulse spectrophotometry. ICG plasma disappearance rate (PDR) and ICG 15-min retention (R15) are proportional to liver function. The aim of this study is to evaluate the efficacy of ICG to assess the hepatic function of patients with constrictive pericarditis who are undergoing to surgical pericardiectomy.

Methods: From 2010 and 2014 ten patients with constrictive pericarditis, who underwent surgical pericardiectomy in our Institution, were enrolled in this prospective observational study. Mean age was 67 ± 7.2 years, Mean EF% was 57 ± 5. Liver function was examined by "LIMON Test" preoperatively and six months after surgery. Serum liver function tests were also measured on the same day.

Results: Both right and left atrial pressures decreased after surgery (Right pressure from 17.1 ± 1.4 mmHg to 8.7 ± 1.5 mmHg; Wedge from 17.8 ± 3.6 mmHg to 10.7 ± 3.5 mmHg). PDR increased from 9.6 ± 1.19 to 18.3 ± 4.2 (p = 0.0156). Conversely, R15 decreased from 26.4 ± 6.3 to 8.94 ± 6.7 (p = 0.0016). Perioperative mortality occurred in the patient with the most low pre-operatively PDR level (2.8) and the most high level of R15 (68). There was one late death due to pulmonary embolism two years later. Serum liver function test were similar between pre-and post-op: aspartate aminotransferase 34.5 ± 12 U/L vs 33 ± 8 U/L; Bilirubin 1 ± 0.4 mg/dL vs 1.4 ± 0.2 mg/dL; alkaline phosphatase 99 ± 59 U/L vs 77 ± 23 U/L (p = n.s).

Conclusions: LIMON Test can be proposed to preoperatively assess the hepatic function, instead of current liver function tests, and as predictor of perioperative mortality in cardiac surgery. Larger sample size are need in order to confirm these findings.

Keywords: *LIMON Test; constrictive pericarditis; surgical pericardiectomy; ICG*

Introduction

The normal pericardium is a thin membrane consisting of fibro elastic tissue and contains a small amount of fluid. The pericardium envelopes the cardiac chambers and under physiological conditions exerts limitation of intrathoracic cardiac motion and acute dilatation, suction filling and balancing right and left ventricular output through diastolic and systolic interactions. When the visceral and/or parietal pericardial layers become thickness, fibrotic, and frequently calcified shell-like pericardium, its loss is elasticity. Constrictive pericarditis (CP) is classical defined as impedance to diastolic filling caused by "fibrotic" pericardium, with or without calcification, which results in chronic refractory congestive heart failure. The aetiology of pericardial disease is often difficult to determine or remains idiopathic [1]. The diagnosis and management of pericardial diseases remain challenging because of the vast spectrum of manifestations and the lack of clinical data. The most common symptoms are related to either fluid overload (e.g. elevated central venous pressure, hepatomegaly, pleural effusion, ascites) or decreased cardiac output (e.g. dyspnoea, fatigue, palpitations). Clinical, echocardiographic, and haemodynamic parameters normally used to perform diagnosis of CP are: ECG, Chest X-ray, 2D echocardiography, Cardiac Catheterisation with "Dip an plateau" or "square root" sign, cardiac computed tomography (CT)/ cardiac magnetic resonance imaging (CMR), and routine blood tests (transaminase value, white blood cell count, serum C-reactive protein concentration) [2]. Actually, there is no ideal real-time and bedside technique for assessing liver function. Traditionally, assessment of liver function and injury is based on static tests, such as serum activities of liver enzymes, protein synthesis of the liver (i.e. albumin) and bilirubin. Bilirubin, physiologically, is a haem product, which after hepatocellular uptake undergoes catalysis and conjugation with glucuronic acid before being excreted into the bile. Hyperbilirubinaemia may be caused by pre-intra or post hepatic pathologies. The serum activities of enzymes may reflect hepatocellular necrosis (e.g. transaminases) or cholestasis (e.g. alkaline phosphatase). Hepatic protein synthesis (e.g. albumin) decreases as an indicator of loss of functional liver cell mass. Static tests are, however, inferior to dynamic tests for assessment of liver function [3]. Dynamic assessment of complex liver functions, such is clearance of substances (indocyanine green; ICG) has been shown to reveal otherwise hidden hepatocellular dysfunction. The ICG is a water-soluble anionic compound that is injected intravenously and binds mainly albumin and b-lipoproteins in the plasma. ICG is taken up by hepatocytes and is later excreted unchanged into the bile. It is not metabolized and dose not undergo enterohepatic recirculation [4].

Methods

From 2010 to 2014 ten patients with constrictive pericarditis, who underwent surgical pericardiectomy in our Institution, were enrolled in this prospective observational study. Inclusion criteria was cardiac surgical procedure in patients admitted for constrictive pericarditis. Exclusions criteria were known hypersensitivity to IG and lack of consent. Written informed consent was obtained from all subjects. Anaesthesia, perfusion and perioperative care were based on institutional standards. Patient were induced with midazolam and maintain with total intravenous anaesthesia with propofol and remifentanil, paralyzed with rocuronium. After orotracheal intubation, a three-lumen central venous catheter (Arrow, reading, PA) was inserted into the right internal jugular vein. Heart rate, arterial blood pressure and central venous pressure were continuously monitored. Arterial oxygen saturation was continuously monitored by pulse oxymetry. The use of inotropes were decided according to the hemodynamic balance and the PA parameters. The CPB use decision was based on haemodynamic instability due to the surgical manipulation and heart contractility. On intensive care unit (ICU), hemodynamic stability, the absence of major bleeding and neurologic complications as well as sufficient pulmonary function were criteria for extubation. All patients underwent measurements with the LIMON-System (PC5000 LIMON Monitor, Liver Monitoring, Pulsion Medical Systems, Munich) preoperative and six months after the operation. For each measurement, IG (0.25 mg/Kg BW) was injected intravenously by peripherical access, and the PDR-ICG (%/min) as well as the R15-ICG (%) were determined via the LIMON oxymetry fingertip sensor. Additionally, serum liver function tests were obtained for each patients on the same day: total Bilirubin (mg/dL), aspartate aminotransferase (U/L), alkaline phosphatase (U/L), Albumin (mg/dL).

Statistical Analyses

Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed values. For univariate analysis, normally distributed continuous variables were compared by Student's t-tests. Statistical significance was defined at two-tailed p value levels of 0.05.

Results

Demographics and early perioperative data are shown in (Table 1). All patients underwent complete (phrenic-to-phrenic) pericardiectomy. The surgical view of approach was median sternotomy. Pericardiectomy was performed on beating heart in 5 pts (50%), in the other 5 pts (50%) CPB was needed to complete pericardium resection. Pericardiectomy without CPB has an established track record for treatment of pericardial constriction [5]. Perioperative PDR-ICG and R15-ICG measurements revealed significant differences between the pre-and post-operatively value. PDR increased from 9.6 ± 1.19 to 18.3 ± 4.2 (p = 0,0156). Conversely, R15 decreased from 26.4 ± 6.3 to 8.94 ± 6.7 (p = 0,0016) (Table 2). Both right and left atrial pressures decreased after surgery and Serum liver function lab tests were similar between pre-and post-op (Table 3). One patient developed renal failure. One patient died in hospital and the cause of death was gastric haemorrhage. That patient had the most low pre-operatively PDR level (2.8) and the most high pre-operatively R15 level (68). One late death, due to pulmonary embolism, occurred 2 years after the procedure (Table 4).

	Patients (n = 10)
Demographics	
Male, n (%)	7 (70)
Age, (years)	66.2 ± 6.5
BSA	1.9 ± 0.17
Clinical data	
Diabetes, n (%)	2 (20)
Hypertension, n (%)	9 (90)
Dyslipidaemia, n (%)	6 (60)
BPCO, n (%)	5 (50)
FAC, n (%)	6 (60)
Aetiology	
Idiopathic, n (%)	3 (30)
Postsurgical, n (%)	1 (10)
Tuberculosis, n (%)	6 (60)
Functional	
NYHA class III/IV, n (%)	5 (50)
Cardiac symptom and signs	
Raised jugular vein distension n (%)	7 (70)
Lower limb edema n (%)	4 (40)
Abdominal distension n (%)	3 (30)
Pleural effusion n (%)	9 (90)
Echocardiographic	
LVEF %, MD ± SD	54 ± 8
LA diameter, mmMD ± SD	43 ± 14
Laboratory pre-op tests	
Serum creatinine (mg/dl)	2 ± 0.34
Serum sodium (mg/dl)	138 ± 4.4
Serum bilirubin (mg/dL)	1 ± 0.4
Aspartate aminotransferase (U/L)	34.5 ± 12
Serum albumin (g/dL)	3.8 ± 1.1
Alkaline phosphatase (U/L)	99 ± 59

Table 1: *Demographic and Perioperative Data of the Study Group.*

value	Pre	Post (at 6 months)	*P*
R15-ICG (%)	2.4 ± 6.3	8.9 ± 6.7	(p = 0.001)
PDR-ICG (%)	9.6 ± 1.19	18.3 ± 4.2	(p = 0.01)

Table 2: *LIMON Test data.*

	Pre	Post	*P value*
Right pressure (mmHg)	17.3 ± 1.9	8.7 ± 1.5	(p = 0.001)
Wedge pressure (mmHg)	17.8 ± 3.6	10.7 ± 3.5	(p = 0.001)
Alkaline phosphatase U/L)	99 ± 59	77 ± 23	ns
Serum bilirubin (mg/dL)	1 ± 0.4	1.4 ± 0.2	ns
Aspartate aminotransferase U/L)	34.5 ± 12	33.8 ± 1.1	ns
Serum albumin (g/dL)	3.8 ± 1.1	3.9 ± 0.42	ns

Table 3: *Pre-operative and post-operative data.*

Hospital mortality, n. (%)	1 (10)
Late death (at 2 years), n. (%)	1 (10)
Renal failure, n. (%)	1 (10)
Intensive care unit stay, days	2 ± 1.37
Hospital stay, days	9 ± 15

Table 4: *Postoperative Data.*

Discussion

Pericardial diseases are not uncommon in daily clinical practice. These syndromes includes acute and chronic pericarditis, pericardial effusion, constrictive pericarditis, and neoplasm. The diagnosis and management of constrictive pericarditis remain challenging because of the vast spectrum of manifestations and the lack of clinical data. The most common symptoms are related to either fluid overload (eg. elevated central venous pressure, hepatomegaly, pleural effusion, ascites) or decreased cardiac output (eg. dyspnea, fatigue, palpitations). Clinical, echocardiographic, and haemodynamic parameters normally used to perform diagnosis of CP are: ECG, Chest X-ray, 2D echocardiography, Cardiac Catheterisation with "Dip an plateau" or "square root" sign, cardiac computed tomography (CT)/ cardiac magnetic resonance imaging (CMR), and routine blood tests (transaminase value, white blood cell count, serum C-reactive protein concentration) [2]. Surgical removal of the pericardium has a significant operative mortality ranging from 6 to 12%. Pericardiectomy must be as complete as is technically feasible [2]. In the literature, the reported incidence of splanchnic hypoperfusion leading to surgical intervention is low (range 0.2 and 2%) [6]. However, mortality in these patients rise as high as 60% [6]. In a study by Sander., *et al*. splanchnic ischaemia and hepatic dysfunction are severe complications after coronary artery bypass grafting (CABG) [8]. Non-invasive determination of the PDR-ICG offers an opportunity for early diagnosis of hepato-splanchnic hypoperfusion. There are only a few devices available to give bedside information in a short period time. The introduction of PDR-ICG offers an opportunity for the early diagnosis of hepatic dysfunction. PDR-ICG values have been validated predominantly in critically ill patients and in patients after liver transplantation. In patients after liver transplantation, the PDR-ICG is used to detect early transplant failure and to monitor transplant function [9]. ICG as a marker of global liver function has been extensively studied in the context of post-operative liver surgery and in the intensive care setting in patients with impending liver failure [10-11] and a predictor factor of mortality in cardiac surgery after CABG, OPCAB and valve surgery [12]. Due to Guha., *et al*. the utilization of a combination of biomarkers and non-invasive global liver function assessment (ICG clearance) may present an attractive strategy for the assessment of liver performance in the Fontan circulation during late follow-up. Malbrain., *et al*. looked that

PDR-ICG is positively correlate to abdominal perfusion pressure and inversely correlate to intra-abdominal hypertension (IAP) [11]. Measurement of PDR may be useful additional clinical tool to assess the negative effects of increased IAP on liver perfusion and function. Similar to the data of Michelet., *et al*. [13], an increase in IAP is associated with a concomitant decrease in PDR-ICG. Weis., *et al*. demonstrate that preoperative PDR-ICG value less than 12.85%/min are associated with an increase incidence of prolonged ICU stay [12]. Kimura., *et al*. show that extremely low PDR-ICG or failure to improve PDR are signs of poor outcome [3]. ICG, a water-soluble tricarboncyanine, is irreversibly removed by hepatocytes in a flow-dependent manner, into bile. Relevant extra-hepatic elimination pathways do not exist. The PDR and R15 measurements are affected by the functioning hepatocyte mass and the volume and rate of blood flow to the liver. They are not closely related with cardiac output per se, because of auto regulation to the splanchnic bed. Elevated central venous pressures are transmitted directly to the hepatic veins and indirectly to the portal circulation.

Conclusion

In conclusion, we found that immediately after pericardiectomy the atrial pressures decrease reducing the liver venous stasis and improving haemodynamic. The combination of these two lead to an improvement of the liver function. After six months PDR-ICG improve and R15-ICG decrease instead hepatic blood tests are always in range. The most relevant limitation to our study is the fact that the data derive from a single center. Fortunately, the aim of the study is to evaluate the efficacy of PDR-ICG and R15 to assess the hepatic function in patient with Constrictive Pericarditis due to surgery. Moreover, the number of the patients is too small to capture complications, we think that PDR-ICG could be used as a predictor of mortality. Conversely, our results can only underline a possible role of PDR-ICG levels as an outcome prediction tool in combination with other data. Multicenter study should be needed.

Bibliography

1. Khandaker MH., *et al*. "Pericardial Disease: Diagnosis and Management". *Mayo Clinic Proceedings* 85.6 (2010): 572-593.
2. Adler Y., *et al*. "2015 ESC Guidelines for the diagnosis and management of pericardial diseases The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)". *European Heart Journal* 36.42 (2015): 2921-2964.
3. Kimura S., *et al*. "Indocyanine green elimination rate detects hepatocellular dysfunction early in septic shock and correlates with survival". *Critical Care Medicine* 29.6 (2001): 1159-1163.
4. Chijiiwa K., *et al*. "Relation of biliary bile acid output to hepatic adenosine triphosphate level and biliary indocyanine green excretion in humans". *World Journal of Surgery* 26.4 (2002): 457-461.
5. TM Tang A., *et al*. "Successful Off-Pump Pericardiectomy and coronary artery bypass in liver Cirrhosis". *Journal of Cardiac Surgery* 20.3 (2005): 284-286.
6. Ohri SK., *et al*. "Cardiopulmonary bypass impairs small intestinal transport and increases gut permeability". *Annals of Thoracic Surgery* 55.5 (1993): 1080-1086.
7. Ott MJ., *et al*. "Postoperative abdominal complications in cardiopulmonary bypass patients: a case-controlled study". *Annals of Thoracic Surgery* 59.5 (1995): 1210-1213.
8. Sander M., *et al*. "peri-opertaive plasma disappearance rate of indocyanine green after coronary artery bypass surgery". *Cardiovascular Journal of Africa* 18.6 (2007): 375-379.
9. Faybik P., *et al*. "Comparison of Invasive and Noninvasive Measurement of Plasma Disappearance Rate of Indocyanine Green in Patients Undergoing Liver Transplantation: A Prospective Investigator-Blinded Study". *Liver Transplant* 10.8 (2004): 1060-1064.
10. Guha I., *et al*. "Structural and functional uncoupling of liver performance in the Fontan circulation". *International Journal of Cardiology* 164.1 (2013): 77-81.

11. Malbrain M., *et al*. "Relation between intra-abdominal pressure and indocyanine green plasma disappearance rate: hepatic perfusion may impaired in critically ill patients with intra-abdominal hypertension". *Annals of Intensive Care* 2.1 (2012): S19.

12. Weis F., *et al*. "Indocyanine green clearance as an outcome prediction tool in cardiac surgery: A prospective study". *Journal of Critical Care* 29.2 (2014): 224-229.

13. Michelet P., *et al*. "Influence of support on intra-abdominal pressure, hepatic kinetics of indocyanine green and extravascular lung water during prone positioning in patients with ARDS: a randomized crossover study". *Critical Care* 9.3 (2005): R251-R257.

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