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► **To cite this version:**

G. Boivineau, J.-M. Gonzalez, M. Gasmi, V. Vitton, M. Barthet. Sphincter of Oddi dysfunction. Journal of Visceral Surgery, 2022, 159 (1), pp.S16-S21. 10.1016/j.jvisc surg.2022.01.008 . hal-04067444

**HAL Id: hal-04067444**

**<https://amu.hal.science/hal-04067444v1>**

Submitted on 22 Jul 2024

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## Sphincter of Oddi dysfunction

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## **Abstract**

Sphincter of Oddi dysfunction (SOD) is a benign non-tumoral disorder of the major papilla. It occurs mainly after cholecystectomy but can also occur before surgery.

Biliary pain and biliary colic are the most frequent symptoms although recurrent pancreatic pain or pancreatitis can also be presenting symptoms.

In about half of the cases, there is a fibrotic stricture of the sphincter of Oddi, probably secondary to the passage of biliary stones, while in the remaining half, the syndrome is due to ampullary motility disorders.

The diagnosis of SOD first requires exclusion of choledocholithiasis or ampullary tumor, by means of ERCP, endoscopic ultrasound or magnetic resonance imaging. Findings on biliary manometry will establish the diagnosis, but this technique is performed less and less often because its high risk of inducing pancreatitis discourages its use as a diagnostic procedure. Biliary scintigraphy offers a risk-free alternative albeit with lower sensitivity

Medical treatment relies on the administration of trimebutine and nitroglycerine when pain occurs. Their efficacy is moderate. Sometimes patients are referred for endoscopic sphincterotomy. Endoscopic treatment should be performed only for patients with biliary pain associated with hepatic function disorders and/or bile duct dilatation. Practicians and patients should be aware that endoscopic sphincterotomy in this clinical setting is associated with a high risk of pancreatitis and its efficacy is limited in patients with pain but without laboratory anomalies or dilatation of the biliary duct (type III Milwaukee classification). Patients with Milwaukee classification type III disorders have mostly functional complaints or psychosocial disabilities and require only medical management.

**Key-words:** Sphincter of Oddi dysfunction, cholecystectomy, biliary pain

## **Abbreviations**

ERCP: endoscopic retrograde cholangio-pancreatography

HDTT: hepatic hilum-to-duodenal transit time

SOD: sphincter of Oddi dysfunction

SO: sphincter of Oddi

## **Definition**

In addition to a randomized study (1) that questioned the role of endoscopic sphincterotomy in the management of sphincter of Oddi dysfunction (SOD), the title of one of the selected summaries in Gastroenterology was « Endoscopic sphincterotomy for sphincter of Oddi dysfunction: inefficacious therapy for a fictitious disease » (2). Under this provocative title lie two realities: 1) endoscopic sphincterotomy should not be the first-line treatment for SOD; 2) although the pathophysiology of SOD is not clearly established, its existence should not be neglected any less than the associated symptoms. Moreover, pain associated with SOD has been specifically characterized in the Rome III and Rome IV classifications (3, 4), as we will see later.

Sphincter of Oddi dysfunction is the name of a syndrome that combines biliary or pancreatic pain of varying degree, liver function test anomalies, and dilatation of the biliary tree secondary to high basal or resting pressure of the Oddi sphincter (SO). The term SOD should replace less appropriate ones found in the literature such as odditis, biliary dyskinesia, Oddi stenosis. Thus, SOD is a motility disorder that affects the SO with biliary and/or pancreatic repercussions. It arises most often (but not exclusively) after cholecystectomy for cholelithiasis (5,6). Most patients with SOD complain of pain similar to that they had before cholecystectomy, and sometimes this pain is even stronger than before.

## **Physiology of the Oddi sphincter pathophysiology**

The Oddi sphincter assures several functions. It provides basal resistance to bile flow while permitting bile excretion (propulsion of bile into the duodenum) as necessary. At the same time, it regulates the storage of bile in the gallbladder. The SO also prevents reflux of duodenal content into the biliary tree. The SO is a true sphincter with permanent basal tonicity that provides a choledochoduodenal pressure gradient with intermittent phasic myogenic contractile activity to force bile flow into the duodenum. The biliary motility activity is coordinated with duodenal motility. Electrical activity increases at the end of the phase II migrant motor complex, reaching a peak during phase III.

The pathophysiology of SOD is complex. Fibrosis of the sphincter is observed in 50 to 60% of patients. Some authors believe that this fibrosis, associated with high basal pressure of the SO, is amenable to endoscopic sphincterotomy but not to medical treatment (5,7). One possible explanation of motility disorders may be denervation

related to cholecystectomy (8) akin to that which occurs during liver transplantation. This denervation results in loss of non-adrenergic, non-cholinergic inhibition of the basal tone of the SO. This loss of inhibition control triggers a cascade of neuromediators such as cholecystokinin (CCK), Vasoactive Intestinal Peptide (VIP) and nitric oxide (NO). Free CCK could then activate the muscular fibers of the SO, thus explaining the paradoxical response to CCK observed during post-cholecystectomy manometry. This type of SOD should normally respond to medical treatment.

Finally, the pathogenic role of biliary cholesterol microcrystals has been suggested. Two studies are not in favor in this theory (9,10). Both of these studies have shown that the prevalence of biliary microcrystals was identical whether the basal pressure of the SO was elevated or not.

### **Pain characteristics**

Biliary pain, localized in the epigastrium and/or right upper quadrant, is defined by precise criteria according to the Rome IV conference (4) : 1) duration of pain > 30 min building up to a steady level; 2) symptoms recurring at different intervals; 3) pain severe enough to interrupt daily activities or lead to an emergency department visit; 4) no relation to bowel movements (<20%) ; 5) not significantly relieved by postural change or acid suppression. Secondary criteria include nausea or vomiting, radiation of pain to the back/right subscapular region and potentially insomnia-generating pain.

The interval between cholecystectomy and the onset of pain is quite variable, ranging from a few months to several years, sometimes even more than 20 years (5,7,11,12). Pain may be triggered by fatty meals or by codeine containing analgesics or antitussives. Intake of codeine is a positive element of diagnosis and must be sought routinely during history taking. Pain can occur spontaneously, and this randomness is a source of major apprehension for patients. Post-cholecystectomy SOD typically presents with biliary symptoms. Post-cholecystectomy pain can be observed in 10-40 % of patients undergoing cholecystectomy (5-8,13-16). The prevalence of SOD is quite variable in published reports ranging from 1.5% to 40 % after cholecystectomy (17,18). Finally, of note, the prevalence of SOD before cholecystectomy is not null in patients with cholelithiasis, ranging from 4% in patients

without bile duct dilatation or liver test anomalies to 40% in patients with elevated alkaline phosphatase (19).

### **Associated symptoms**

Nausea and vomiting can occur with SOD. Some patients have described prolonged episodes of asthenia post-attack (3,5,11,12). SOD is often accompanied by other gastro-intestinal disorders such as irritable bowel syndrome (1,20).

Pain can be associated with elevation of transaminases and alkaline phosphatase that return to normal after the attack. The presence of liver function test anomalies and their threshold of elevation are part of the Milwaukee classification, first published in 1988 and revised in 2004 (7,21). A new nomenclature was proposed during the Rome IV conference (4), which we will deal with later. Transaminase levels can exceed 20 times the upper limit of normal prior to the attack.

SOD has been reported to be a cause of recurrent bouts of acute pancreatitis, generally considered as an idiopathic chronic pancreatitis (5,22,23). Severe acute pancreatitis within the framework of pancreatic SOD has never been reported in the literature (see further). The clinical picture is therefore one of mild to moderate recurrent attacks of acute pancreatitis. Such manifestations could involve up to a quarter of patients with post-cholecystectomy pain.

Finally, SOD occurs in a particular context. The female/male sex ratio ranges from 80 to 90%, as in other functional gastro-intestinal disorders (11,12,24). Although no direct relationship has been established, SOD often occurs in a psychiatric context in patients who suffer from anxiety, depression, antecedent history of sexual abuse, all of which intensify the patients' perception of pain but should not call into question the reality or their fear of pain attacks (20). In a study of patients included in a randomized study, 21% had severe psychiatric disorders. Although there was no clear correlation with the type of symptoms, pain was more intense in the more depressive patients (20). In the management of these patients, it is important to explain the origin of the disorders and not to deny their reality, while warding off the « specter » of endoscopic sphincterotomy.

### **Diagnosis of SOD**

For patients with post-cholecystectomy pain, after eliminating the diagnoses of residual common bile duct stones or an ampullary obstacle by endoscopic ultra-sound

and magnetic resonance imaging (MRI), one can reasonably envision the diagnosis of SOD and evaluate it according to the Milwaukee classification. The initial version included, among other criteria, delayed emptying of the gallbladder after ERCP (>45 min) (21). This classification was modified in 2004 and this criterion was deleted to avoid performance of diagnostic ERCP with its attendant morbidity (7). The modified classification includes three criteria: a) pain seemingly of biliary origin; b) greater than two-fold elevation of SGOT or alkaline phosphatase values observed at least twice; c) increased bile duct diameter (> 12 mm) (7). SOD, diagnosed by manometry, is found in 86% of patients with Milwaukee type I (criteria a+b+c), in 55% with type II (a+ (b or c)), and 28% of type III (only a) (5,7). The diagnostic and therapeutic strategy for SOD is based on this classification. Effectively, it is not acceptable to propose ERCP sphincterotomy to patients with type III SOD, for whom it will be of no use in 75% of cases.

Another study highlighted the possibility of a fourth type of SOD: painless SOD, characterized by the presence of cholestasis or acute hepatocytolysis, for which endoscopic sphincterotomy would be effective, while acknowledging that recurrence can be as high as in classical SOD (25).

It is of note, however, that the Rome IV conference classification has abandoned the Milwaukee classification in favor of another nomenclature: type I corresponds to SO stenosis, type II to functional disorders of the SO (patients with post-cholecystectomy pain and associated objective findings) and type III to functional biliary type pain alone. The Rome IV diagnostic criteria for SO biliary functional disorders (Milwaukee type II) should include: a) biliary type pain; b) elevation of liver enzymes (Twice-normal SGOT or alkaline phosphatase measured at least twice), or dilatation of the common bile duct >12 mm, but not both; c) absence of common duct stones or other structural anomaly; associated criteria include normal lipase or amylase levels, abnormal Oddi manometry, or abnormal biliary excretion on scintigraphy (4). For clarity's sake, we decided to maintain the Milwaukee classification throughout the remainder of this update.

Complementary investigations are warranted in addition to endoscopic ultrasound and bilio-pancreatic MRI, which are needed to eliminate other differential diagnoses (). These include SO manometry and biliary scintigraphy. Before providing the details of these two investigations, we must point out that SO manometry is no

longer practiced in Europe (whereas it is still used in the United States) because of the approximately 10% risk of pancreatitis, which is felt to be unacceptable for a diagnostic test, while the less morbid biliary scintigraphy has a good positive predictive value but low sensitivity.

Biliary manometry (Figure 1), which consists of duodenoscopic trans-ampullary introduction of a pressure catheter into the bile duct, was long the reference diagnostic investigation for SOD. Most centers have abandoned it because of its invasive character, and a 6-11% risk of pancreatitis (5,26). The main diagnostic criterion is an elevated basal SO pressure (>40 mmHg) but other motility criteria should also be considered related to the frequency and propagation of phasic contractions.

Because biliary manometry is difficult to perform, has imperfect reproducibility (50%) (27), and, above all, has a non-negligible risk of post-procedure acute pancreatitis, biliary cholescintigraphy, a completely innocuous method, has been developed. This consists of intra-venous injection of a derivative of di-iminoacetic acid or one of its analogues, tagged with Technetium 99, followed by gamma-camera imaging for 60 min and is reusable after 15 min. The transit time from hepatic hilum to duodenum (HDTT), the main scintigraphic parameter, which correlates best to SO basal pressure, should not exceed six minutes (Figure 2). Cholescintigraphy can be used to distinguish between symptomatic and asymptomatic patients. Likewise, HDTT seems to correlate well with common bile duct diameter. It has also been found to be predictive of the outcome of SO sphincterotomy in small series of patients with SOD (28-32).

Biliary scintigraphy with measurement of HDTT is a good investigation, although there are discrepancies in the literature: low sensitivity for some (32), low specificity for others (28). Nonetheless, cholescintigraphy is non-invasive and reliable. A negative result, however, does not exclude the diagnosis of SOD.

In practice, after elimination of other disorders by endoscopic ultrasound and biliopancreatic MRI, patients can be categorized according to the revised Milwaukee classification that requires clinical evaluation of pain, measurement of liver function tests, and abdominal ultra-sound. This investigative panel assesses the overall probability of SOD; the diagnosis is confirmed by cholescintigraphy.

### **Particular case of SOD with pancreatic manifestations**

SOD can also be a cause of recurrent acute pancreatitis in adults as well as in children, although its prevalence is unknown (32-35). This should be a diagnosis of exclusion, and the usual causes should be sought by endoscopic ultrasound and biliopancreatic MRI to eliminate chronic pancreatitis or anatomic anomalies, while a genetic profile is performed to detect PRSS1, SPINK1 and CFTR mutations. In an endoscopic ultrasound study looking for causes of idiopathic acute pancreatitis (37), 27% had chronic pancreatitis and 47% had microlithiasis; overall, a positive diagnosis of SOD was found in 39% of patients. In the presence of pancreatic manifestations that can be attributed to SOD (idiopathic recurrent acute pancreatitis), which are observed in 10-25% of cases, the Milwaukee classification, based on the same principles (5,22), includes three criteria: a) pancreatic type pain; b) > 2X elevation of amylase or lipase; c) diameter of the main pancreatic duct > 6 mm.

According to the Rome IV conference, diagnostic criteria that favor the diagnosis of pancreatic SOD should include: a) documented episode of recurrent pancreatitis (typical pancreatic pain with amylase or lipase elevation > 3X normal and/or imaging evidence of acute pancreatitis); b) exclusion of other etiologies of pancreatitis; c) negative endoscopic ultrasound and d) abnormal SO manometry (4). These new diagnostic criteria imply performance of pancreatic SO manometry, which is no longer performed often because of the risk of post-operative complications.

Final diagnosis requires documentation of a hypertensive pancreatic sphincter, which requires pancreatic manometry, often difficult to perform and which presents a risk of complications even higher than that for biliary manometry. Elevated pancreatic duct pressure is observed in 35 to 80% of patients who have high basal SO pressure. Dynamic ultrasound imaging of the main pancreatic duct after injection of secretin is another possible diagnostic test (33,34). The diagnosis of SOD is confirmed when ultrasonic measurement of main pancreatic duct dilatation exceeds 1 mm after perfusion of 1 IU/Kg of secretin. The ultrasound secretin test is useful not only as a diagnostic test but it also is predictive for the response to surgical sphincteroplasty: the test is positive in patients with SO stenosis or motility disorder. The sensitivity and specificity of the test are controversial in the literature with sensitivity variations ranging from 57 to 88 % (33,34). Of note, cholescintigraphy is of no use in the diagnostic approach.

**In practice, there are no complementary investigations that can affirm the diagnosis of pancreatic SOD. The diagnosis is one of exclusion and requires high-quality investigations.**

### **Main differential diagnoses and sources of diagnostic confusion**

The main entities to exclude in the differential diagnosis are retained common bile duct stones followed by ampulloma (5% of patients) and post-cholecystectomy gastro-intestinal motility disorders. The diagnostic work-up should include duodenoscopy, endoscopic ultrasound and biliopancreatic MRI. Only when this workup is completely normal can the diagnosis of SOD can be entertained.

Post-cholecystectomy gastric or duodenojejunal motility disorders, whether associated with SOD or not, have been found with frequent anomalous phase II and III migrant motor complexes. In some cases, duodenojejunal motricity anomalies were present before cholecystectomy (8). Barostatic studies have shown disorders of duodenal sensitivity in patients suspected of post-cholecystectomy SOD (38). The sensitivity disorders were found essentially in the duodenum while barostatic studies of the rectum was normal. This type of duodenal sensitivity or motility disorder may largely explain the post-cholecystectomy pain observed in patients who have neither bile duct dilatation nor hepatic function anomalies, that is in patients with Type III Milwaukee SOD. Confusing these patients with those with true Oddi dysfunction would run the risk of leading to inopportune and potentially dangerous endoscopic procedures.

### **Treatment of SOD**

Evaluation of therapeutic efficacy is clouded by several confounding factors, mainly related to the difficulty in the diagnosis of SOD, to the incomplete understanding of the pathophysiology of SOD (particularly Milwaukee types III where functional digestive disorders are associated), as well as to the psychological context where it may be difficult to interpret the symptoms expressed by the patient. Thus, the two first randomized trials that favored the use of endoscopic sphincterotomy included patients with type II SOD (39,40), while the last randomized trial, that included 90% of patients with type III SOS, did not (1).

Medical treatment of SOD has been disappointing even though certain publications have shown that nitrate medications and calcium channel blockers

decrease the SO basal pressure (11,41). Nitroglycerin is used mainly as sprays administered during the acute phase of pain, that have proved effective in more than 75% of patients, with side-effects of headache or drop in blood pressure. Their efficacy for pain relief is reassuring for patients. Other treatments have shown encouraging results including duloxetine, amitriptyline or phosphodiesterase type-5 inhibitors (4,42,43). Trimebutine, which regulates both SO and duodenal motricity disorders, is also useful for prevention of attacks (11). However, the most essential preventive measure, combining trimebutine and nitroglycerin, whose use must be well explained to the patient, leads to symptom relief in 75% of patients at one year (12) and constitutes the pillar of medical management.

Endoscopic treatment is reserved for patients with failure of medical management, keeping in mind the risk of post-operative pancreatitis and the debatable durability of efficacy in patients with type III SOD (12,44).

Intrasphincteric injection of botulinum toxin has been tested in both porcine and human models (45,46). Injection of botulinum toxin A led to a significant drop in basal SO pressure in 50% of patients. From the clinical viewpoint, intrasphincteric injection was associated with improvement in 55% of patients with post-cholecystectomy biliary pain without hepatic enzymatic or common bile duct anomalies. However, symptoms recurred within six months in 90% of patients who had shown improvement. The effect of Botulinum toxin is therefore inconstant and transient. Although it can be used to predict the response to endoscopic sphincterotomy (47), it has been abandoned as medical treatment of SOD in this setting.

ERCP sphincterotomy can be effective in patients with SOD demonstrated by manometry or cholescintigraphy, but is associated with high morbidity, essentially post-operative pancreatitis. The 2014 update of the European guidelines highlighted SOD as the main risk factor for post-ERCP pancreatitis (48). This complication should be prevented by administration of nonsteroidal anti-inflammatory drugs, preferably *per rectum*, associated whenever possible with the insertion of a 5 Fr pancreatic duct stent (47) and eventually vigorous intra-venous hydration. Two randomized studies have shown symptom relief in 90% of patients (39,40). Of note, most patients in these studies had Milwaukee type II SOD (23). The therapeutic response to biliary sphincterotomy has been reported to depend on the type of SOD, with the best response in type I, then type II and finally the least response in type III SOD (5). Likewise, in the third and most recent EPISOD randomized study, that included 90%

of patients with Milwaukee type III SOD, the success rates were 37% for the active treatment arm vs. 23% for the sham procedure (1). This result, which stirred a great deal of impassioned outcry from the international scientific community, leading some to challenge the very concept of SOD, was easily predictable. The prevalence of basal SO hypertension in the group of patients with SOD was 28% (5), which corresponds to the efficacy found in this series. This study concluded that endoscopic treatment should not be proposed for type III SOD patients, even more since the long-term results of the EPISOD 2 study confirmed these outcomes at five years (49).

The problem of deciding the indications for ERCP pancreatic sphincterotomy is complex. The EPISOD study reported that the outcome after a double (biliary and pancreatic) sphincterotomy did not provide any statistically significant benefit in patients with pancreatic sphincter hypertension (30% vs. 20% for simple biliary sphincterotomy) (1). Another randomized study on the efficacy of pancreatic sphincterotomy included 69 patients with idiopathic recurrent acute pancreatitis (50); half of the patients underwent ERCP biliary sphincterotomy alone and the other half underwent double (biliary and pancreatic) sphincterotomy. After a mean follow up of 78 months, half the patients in each group still had intermittent attacks of acute pancreatitis. Moreover, 17% of patients developed chronic pancreatitis in the interval. This study illustrates the problem of establishing a clear-cut diagnosis of pancreatic SOD, since in at least half of the patients, pancreatitis occurred on a background of underlying disease, as already suggested by other studies such as endoscopic ultrasound or detection of genetic mutations (37). Prudence is still very much warranted in the diagnosis and treatment of pancreatic SOD.

Among predictive factors of efficacy, immediate elevation of liver function tests after pain was found to be predictive of a favorable response to sphincterotomy, while bile duct dilatation was not (51). Many patients classified as Milwaukee type II and above all type III do not have SOD but rather duodenal motility or sensitivity disorders. The long-term durability of the outcome of ERCP sphincterotomy has not been often evaluated, as the follow-up of most studies is limited to one year. We compared the results of ERCP sphincterotomy to those of medical treatment with trimebutine plus nitroglycerin (44). Of the 59 patients included, 57% and 19% had type II and type I disorders, respectively. At one year, 71% of patients were treated medically while only 24% had endoscopic treatment. The early therapeutic efficacy was 64% vs. 86 %

compared to 62 % vs. 64 % at 30 months. These results show that endoscopic treatment can provide short-term relief for selected patients, but this difference is not durable over time. This is another argument to be considered in the therapeutic decision.

The therapeutic sequence should be based on initial medical management, with avoidance of opioids, administration of trimebutine as maintenance therapy and nitroglycerin during attacks for one year (11,12,44). The patient should be informed of the risk of potential inefficacy of endoscopic management. Psychological and clinical follow-up are essential during this period. At one year, treatment failure is expected in one out of four patients and endoscopic treatment can then be proposed but the patient must be informed on the risk of complications as well as possible long-term waning efficacy (44).

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Figure 1: Biliary manometry: duodenal pressure was used for the zero reference point. The catheter is first positioned in the bile duct (cholechooduodenal gradient) then withdrawn to the Oddi sphincter (phasic contraction and basal pressure) then repositioned in the duodenum

Figure 2: Biliary scintigraphy: hilum–duodenum transit time (HDTT) (in this example: 10 min therefore prolonged (> 6 min))

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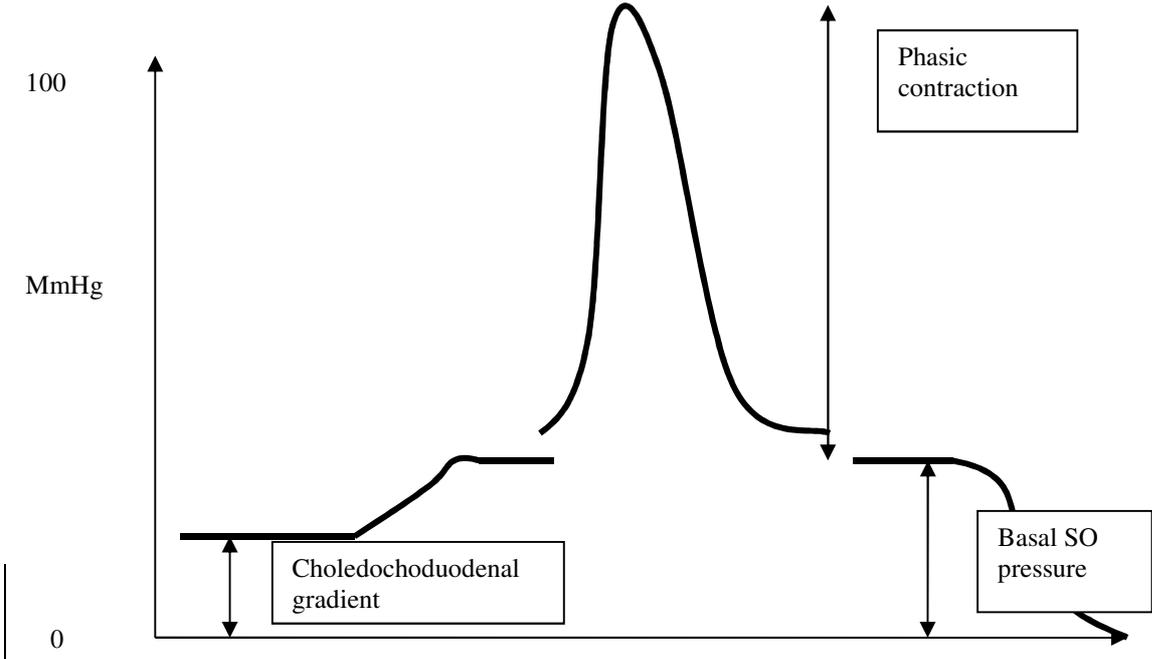


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