

Chronic pancreatitis: A surgical disease? Role of the Frey procedure

Alexandra Roch, Jérôme Teyssedou, Didier Mutter, Jacques Marescaux, Patrick Pessaux

Alexandra Roch, Jérôme Teyssedou, Didier Mutter, Jacques Marescaux, Patrick Pessaux, Digestive and Endocrine Surgery, Nouvel Hôpital Civil, University of Strasbourg, 67000 Strasbourg, France

Alexandra Roch, Jérôme Teyssedou, Didier Mutter, Jacques Marescaux, Patrick Pessaux, Institut de recherche en cancérologie de l'appareil digestif (IRCAD), 67000 Strasbourg, France
Alexandra Roch, Jérôme Teyssedou, Didier Mutter, Jacques Marescaux, Patrick Pessaux, IHU-Strasbourg, Minimally-Invasive Image-Guided Surgical Institute, University of Strasbourg, 67000 Strasbourg, France

Author contributions: All the authors contributed to this paper.
Correspondence to: Patrick Pessaux, MD, PhD, Professor, Head of the Hepatobiliary and Pancreatic Surgical Unit, Digestive and Endocrine Surgery, Nouvel Hôpital Civil, University of Strasbourg, 1 place de l'hôpital, 67000 Strasbourg, France. patrick.pessaux@chru-strasbourg.fr
Telephone: +33-3-69551563

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Abstract

Although medical treatment and endoscopic interventions are primarily offered to patients with chronic pancreatitis, approximately 40% to 75% will ultimately require surgery during the course of their disease. Although pancreaticoduodenectomy has been considered the standard surgical procedure because of its favorable results on pain control, its high postoperative complication and pancreatic exocrine or/and endocrine dysfunction rates have led to a growing enthusiasm for duodenal preserving pancreatic head resection. The aim of this review is to better understand the rationale underlying of the Frey procedure in chronic pancreatitis and to analyze its outcome. Because of its hybrid nature, combining both resection and drainage, the Frey procedure has been conceptualized based on the pathophysiology of chronic pancreatitis. The short and long-term outcome, especially pain relief and quality of life, are better after the Frey procedure than after any other surgical proce-

cedure performed for chronic pancreatitis.

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Key words: Chronic pancreatitis; Frey procedure; Surgery; Complication; Outcome

Core tip: The management and the treatment of chronic pancreatitis are challenging. Many surgical procedures were described with 2 different types of concepts: resection vs drainage. The Frey procedure is an association of these 2 concepts. This manuscript contains the most recent data about the technique, the short and long-term outcomes of this technique. In addition, there is a review of the literature of series comparing this technique with the other surgical procedures.

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INTRODUCTION

Chronic pancreatitis is a progressive inflammatory disease characterized by debilitating pain and pancreatic insufficiency (nutritional deficiency and glucose deregulation)^[1,2]. The enormous personal and socioeconomic impact comprises impairment of quality of life, inability to work and even shortening in life expectancy^[3]. Although medical treatment and endoscopic interventions are primarily offered to patients with chronic pancreatitis^[4,5], approximately 40% to 75% will ultimately require surgery during the course of their disease^[6,7].

Although pancreaticoduodenectomy has been considered the standard surgical procedure for patients with chronic pancreatitis because of its favorable results

on pain control, its high postoperative complication and pancreatic exocrine or/and endocrine dysfunction rates^[8,9] have led to a growing enthusiasm for duodenal preserving pancreatic head resection^[10,11]. When in 1987 Frey *et al.*^[12] described a novel hybrid procedure combining local resection of the head of the pancreas and longitudinal pancreatico-jejunostomy, surgeons favorably welcomed it because of its technical feasibility and low surgical risk. Since 1987, numerous studies have analyzed the short and long-term outcome following the Frey procedure and have compared it to other surgical procedures commonly performed for chronic pancreatitis. The aim of this review is to better understand the rationale underlying of the Frey procedure in chronic pancreatitis and to analyze its outcome.

WHY CAN CHRONIC PANCREATITIS BE CONSIDERED A SURGICAL DISEASE?

Mechanisms of pain in chronic pancreatitis

Although pain is the most common symptom (85% of patients)^[2] in chronic pancreatitis, its mechanism remains unclear and debated^[13-15]. Several concepts have been hypothesized and pain probably results from a combination of them. The intraductal and interstitial hypertension theory is similar to a compartment syndrome^[16,17]. Increased ductal pressure related to duct stricture or calculi and intraparenchymal hypertension as a result of fibrosis and edema can activate intrapancreatic nociceptors. The neurogenic theory focuses on intrapancreatic neural damage^[18]. Inflammatory mediators from infiltrating lymphocytes are responsible for increased signals along the axons of pain-sensitive neurons, which ultimately can result in a “centrally sensitized” pain state^[19]. Traditionally, the head of the pancreas is called the “pacemaker” of pain in chronic pancreatitis. It is often enlarged and can be replaced by an inflammatory mass that can lead to common bile duct or duodenal stenosis^[20]. Another explanation to this pain is the compression of adjacent organs by a pseudocyst.

Indications for surgery

Surgical management is usually offered to patients after medical treatment and endoscopic intervention have failed^[4,5], and is considered the last option of this step-up approach^[21]. Medical treatment for pain related to chronic pancreatitis usually fails, as narcotic dependency occurs in most patients^[11]. Longitudinal studies have shown that 40% to 75% of all patients with chronic pancreatitis will require surgery in the course of the disease^[7]. The main indications for surgery are intractable pain, non-resolving common bile duct or duodenal stenosis and suspicion of malignancy. The objective of surgery is to relieve intractable pain while preserving pancreatic endocrine and exocrine functions.

Rationale for surgery in chronic pancreatitis

First, surgery has been proved superior to endoscopic

treatment in 2 main randomized controlled trials^[22,23]. Moreover, several studies have suggested that surgery early in the course of chronic pancreatitis is beneficial in terms of pain control and pancreatic function^[21,24]. One experimental and three clinical observational cohort studies have concluded that surgery, especially drainage procedures, can delay the natural course and progressive loss of pancreatic function in chronic pancreatitis. In an experimental model of early *vs* late surgical drainage in pigs, early surgery resulted in less pathological cell damage and better exocrine function^[25]. When Nealon *et al.*^[26] compared the outcomes of conservative treatment *vs* surgery, they reported a delay in pancreatic function impairment after surgical treatment. They concluded that early operative drainage should be performed before the pancreas shows morphological and functional irreversible damage. Ihse *et al.*^[27] also have recommended surgical treatment to be performed before nutritional or metabolic disorders develop.

Prolonged periods of pain can be associated with peripheral and central nerve sensitization, leading to a permanent state of pain impossible to reverse^[19]. A recent observational study suggests that longstanding disease is associated with poor pain control after surgical intervention^[28]. In 266 consecutive patients undergoing surgery for chronic pancreatitis, surgery after 3 years of onset of symptoms was independently associated with impaired pain relief and increased rate of endocrine pancreatic insufficiency. A small pilot trial randomized 32 patients with early stage chronic pancreatitis and dilated pancreatic duct between upfront surgical drainage and conservative approach^[29]. Significant pain relief was observed in 94% patients in the surgical group compared to 13% patients in the conservative group. New onset pancreatic insufficiency was significantly less frequently observed in the early surgical group compared conservative group. Despite the evidence suggesting a benefit of early surgery, most patients are still managed by a conservative step-up approach. To evaluate the benefits, risks and costs of early surgical intervention, the Dutch Pancreatitis Study Group is currently conducting a multicentric randomized controlled trial (the Early Surgery *vs* Optimal Current Step-up Practice for Chronic Pancreatitis trial)^[21].

The role of chronic pancreatitis as a risk factor for pancreatic carcinogenesis has been supported by numerous studies since 1993^[30-32]. Lowenfels *et al.*^[30] published an international cohort study of 2015 patients that reported a cumulative risk of pancreatic cancer in subjects with chronic pancreatitis of 1.8% after 10 years and 4%, after 20 years with a standardized incidence ratio of 14.4. A recent multicentric Japanese study^[33] of 506 patients found that the incidence of pancreatic cancer was significantly lower in patients who underwent surgery for chronic pancreatitis than in patients who had a conservative treatment (0.7% *vs* 5.1%, $P = 0.03$, HR = 0.11). Although this study shows a protective effect of surgery in the development of pancreatic cancer from chronic pancreatitis, the exact mechanism remains unclear probably through reduction in pancreatic inflammation.

FREY PROCEDURE: SURGICAL TECHNIQUE

Rationale for the Frey procedure

Based on the pathophysiological mechanisms described above^[13-19], two main surgical procedure types have been described in patients with chronic pancreatitis: drainage and resection procedures^[11,34,35]. Until the late 80s, pancreaticoduodenectomy was the resection procedure of choice for “head-dominant” disease^[11]. The Frey procedure was first described in 1987 by Frey *et al*^[12] and combines partial resection of the head of the pancreas (resection) with lateral pancreatico-jejunostomy (drainage). The rationale for this hybrid procedure^[12,36-38] is that it improves the overall pancreatic ductal drainage by decompressing both the duct of Santorini and ducts in the uncinate process. It also allows removal of calculi. Moreover, the partial pancreatic head resection removes what is thought to be the “epicenter” of chronic pain and can relieve symptoms related to ductal stricture.

The Frey procedure was originally applied to patients with an enlarged fibrotic head of the pancreas and an associated dilated main pancreatic duct. It has since then been described in various indications, including patients who have had prior lateral pancreatico-jejunostomy (Puestow or Partington and Rochelle procedures) with no relief of symptoms^[38].

Surgical technique

Through a bilateral subcostal incision and after exposure of the pancreas (Kocher maneuver), the main pancreatic duct is located using a syringe aiming toward the tail of the pancreas^[12,36-40]. The pancreatic duct is then opened longitudinally (the incision in the tail of the pancreas is extended to within 1-2 cm of the distal portion of the gland and the incision in the head to within 1 cm of the inner aspect of the duodenum). When the main pancreatic duct is exposed, it can be inspected and all calculi removed. The head of the pancreas is partially cored-out while preserving a rim of pancreatic tissue along the inner aspect of the duodenum (to allow blood supply to the duodenum from superior and inferior pancreaticoduodenal arteries), along the pancreatic medial margin (to avoid injuring the superior mesenteric/portal vein) and posteriorly (between the head excavation and the uncinate process and vena cava). During the local excision of the head of the pancreas, the intrapancreatic portion of the common bile duct is freed from inflamed and fibrotic periodical tissue. In about 70% of cases, resection of the fibrotic pancreatic parenchyma is sufficient to relieve a common bile duct stricture. If the obstruction cannot be relieved, a choledocho-duodenostomy or a choledocho-jejunostomy can be performed. The cored-out head of the pancreas and the open main duct are drained into Roux-en-Y limb of jejunum. The Roux-en-Y limb is passed through the transverse mesocolon to lie over the pancreas. A two-layer pancreatico-jejunostomy is performed. The gastrointestinal tract continuity is restored

by and end-to-side jejunio-jejunostomy. Owing to the increased risk of pancreatic cancer in patients with chronic pancreatitis, the cored tissue from the pancreatic head is routinely sent for pathological analysis.

Technical key points

Compared to other surgical procedures (especially pancreaticoduodenectomy and Beger procedure), the Frey procedure is easier to perform by avoiding the transection of the pancreas neck over the superior mesenteric/portal vein.

Although Frey *et al*^[37-39] analyzed the relation between weight of the cored pancreatic head tissue and pain relief, this amount of tissue depends on the size of the head of the pancreas, which is highly variable. Some studies suggested that a mean volume percent of head mass resected between 60% and 65% allowed better pain relief. Extensive pancreatic head excision should not be performed as it may lead to increased parenchymal loss and ultimately pancreatic exocrine insufficiency.

Current data suggest that the Frey procedure in small duct chronic pancreatitis is associated with a significantly increased operative time^[41]. Difficulty in locating the main pancreatic duct contributes to the delay and intra operative ultrasound in those cases proves useful^[42].

Because the Frey procedure can be technically challenging due to major chronic inflammation, it is traditionally performed as an open surgery. Surgeons from John Hopkins recently published a case report describing a total laparoscopic Frey procedure for chronic pancreatitis caused by recurrent pancreatic ductal stones^[43]. The laparoscopic approach confers the benefits of magnified visualization while reducing the rate of postoperative wound infection, incisional hernia, bowel obstruction and pain^[44]. As laparoscopic Frey procedure is very demanding, the selection of patients that can benefit from it is very important. This approach will less likely be offered to obese patients, as visualization can be impaired by retroperitoneal fat. Similarly, this approach does not fit patients with a highly vascular head of the pancreas because of the increased risk of bleeding.

RESULTS OF THE FREY PROCEDURE

Complications

The Frey procedure can be performed with low mortality (< 2%). The published complication rates range from 7% to 42%^[45-50]. The most common complications include hemorrhage, pancreatic fistula and intra-abdominal abscess. Arterial bleeding is the major life-threatening complication (2%-3%). It can occur several days from surgery after erosion of per pancreatic vessels by pancreatic fluid from an anastomotic leakage, or due to the rupture of a pseudoaneurysm^[41,49]. Late complications rate after the Frey procedure is high, probably because of comorbidities (alcohol, smoking) in most patients with chronic pancreatitis. The main medical complication is pulmonary infection and/or insufficiency^[50]. In 2006, Pessaux *et al*^[49]

recommended preoperative respiratory physiotherapy for all patients before the Frey procedure to avoid postoperative respiratory complications.

Short and long-term outcome

Exocrine insufficiency has been described in up to 79% of patients following the Frey procedure, whereas de novo diabetes occurs in only 8% to 34% of patients^[45-50].

Keck *et al.*^[47] showed that 62% of patients were completely pain free 5 years after the Frey procedure. Similarly, Negi *et al.*^[51] showed that the Frey procedure led to significant and sustained complete or partial pain relief in 75% over a median follow-up of 6 years. This study suggests that the Frey procedure significantly decreases the severity of recurrent exacerbations and also the number of acute episodes requiring hospital readmission. Falconi *et al.*^[52] reported up to 90% of partially or completely pain-free patients after the Frey procedure. Hildebrand *et al.*^[53] showed that the indices for global quality of life and for physical and emotional status increased after the Frey procedure.

Factors predicting outcome

Ten to 20% of patients demonstrate persistent pain after the Frey procedure^[44-50]. Several risk factors for poor pain relief have been described in the literature, with controversial results^[54]. In 1999, Frey and Amikura^[38] found that chronic narcotic use, multiple abdominal interventions before pancreatic surgery were associated with poor outcome, whereas Riediger *et al.*^[55] found that preoperative exocrine insufficiency and postoperative surgical complications were the strongest predictors of poor pain relief. In an Indian study^[41], preoperative use of opiates, continuous pattern of pain and postoperative complications were significant predictive factors of failure to achieve complete pain relief after surgery. However, even patients who used opiate medication preoperatively benefited from surgery (significant reduction in pain score, number of pain exacerbation and hospital readmissions). These results suggest that preoperative narcotic use should not be considered a contraindication to the Frey procedure although patients should be referred for surgery early in the course of chronic pancreatitis before drug addiction becomes an issue.

The correlation between main pancreatic duct diameter and pain relief after the Frey procedure remains debated^[38,56,57]. A recent study from John Hopkins showed that the degree of pancreatic fibrosis correlated with the resolution of pain in a series of 35 patients treated with the Frey procedure^[58]. Their results suggest that pain in patients with extensive pancreatic fibrosis is significantly better relieved by the Frey procedure than in patients with mild or minimal fibrosis. They implied that patients with mild or minimal fibrosis may respond more favorably to other procedures such as total pancreatectomy with islet auto-transplantation. Determination of pancreatic fibrosis extent preoperatively, thanks to improving imaging technologies, might be an important variable to

choose the surgical procedure more likely to achieve pain relief. They also found an association between ductal dilation ≥ 4 mm and better pain relief. However, they believe that the influence of main pancreatic duct diameter on outcome following the Frey procedure may be biased, as ductal dilation is usually the consequence of progressive fibrosis. In these cases, an alternative could be an extended drainage by “V-shaped excision” advocated by Izbicki *et al.*^[59] and Yekebas *et al.*^[60] with a partial head resection. This technique seems to be a secure and effective approach for small duct chronic pancreatitis achieving significant improvement in quality of life and pain relief.

Comparison Frey vs other surgical procedures for chronic pancreatitis

Frey procedure vs pancreaticoduodenectomy: Operation time is shorter with the Frey procedure, with lower intraoperative blood loss and perioperative transfusion requirements^[61]. Chiang *et al.*^[62], in a prospective study comparing the Frey procedure to pancreaticoduodenectomy found no difference in mortality, morbidity, pain relief or improvement in pancreatic function 3 and 6 mo after surgery. One randomized controlled trial including 61 patients compared the outcome of pancreaticoduodenectomy and Frey procedure^[63]. In this trial (follow-up of 2 years), Izbicki *et al.*^[63] found better results after Frey procedure regarding quality of life, although pain relief was similar after both procedures. Additionally, the rate of complications after the Frey procedure was significantly lower than after pancreaticoduodenectomy (19% *vs* 53%). Farkas *et al.*^[64] supported those results concluded that the Frey procedure led to better long-term quality of life. In the long-term follow-up study (mean of 7 years) published by Strate *et al.*^[65], there was no difference between Frey and pancreaticoduodenectomy regarding late mortality, survival rate, exocrine and endocrine insufficiency (although the rates of new onset diabetes after both procedures were twice higher than preoperatively) and need for reintervention. The initial favorable results of quality of life and pain after Frey procedure still existed but were not statistically significant. Interestingly, Aspelund *et al.*^[66] found however a significantly lower incidence of new onset diabetes after the Frey procedure (8%) than after pancreaticoduodenectomy (25%). A recent randomized controlled trial presented at the European Surgical Association in 2013 reported the 15-year follow-up of the Frey procedure *vs* pancreaticoduodenectomy for chronic pancreatitis^[67]. They concluded that long-term pain relief was comparable after both surgical procedures but the quality of life was better after the Frey procedure. Moreover, mean survival was significantly shorter after pancreaticoduodenectomy because of a higher delayed and long-term mortality rate. Regarding weight gain and work rehabilitation, the Frey procedure also showed better outcome than pancreaticoduodenectomy^[53] (Table 1).

Frey procedure vs Beger procedure: A randomized controlled trial comparing the Frey procedure with Be-

Table 1 Main studies comparing surgical procedures for chronic pancreatitis

Ref.	Year	Study design	Comparison	Median follow-up (in months)
Izbicki <i>et al</i> ^[63]	1998	Retrospective	Frey vs PPPD	24
Aspelund <i>et al</i> ^[66]	2005	Retrospective	Frey vs PD	36
Hildebrand <i>et al</i> ^[53]	2010	Retrospective	Frey vs PD	50
Farkas <i>et al</i> ^[64]	2006	Prospective	Frey vs PPPD	24
Chiang <i>et al</i> ^[62]	2007	Prospective	Frey vs PD	6
Strate <i>et al</i> ^[65]	2008	Prospective	Frey vs PPPD	84
Bachmann <i>et al</i> ^[67]	2013	Prospective	Frey vs PD	180
Izbicki <i>et al</i> ^[46]	1995	Prospective	Frey vs Beger	18
Strate <i>et al</i> ^[68]	2005	Prospective	Frey vs Beger	104
Keck <i>et al</i> ^[47]	2010	Retrospective	Frey vs Beger	20.6

PPPD: Pylorus-preserving pancreaticoduodenectomy; PD: Pancreaticoduodenectomy.

ger procedure^[46] found that the Frey procedure was associated with a lower complication rate (9% vs 15%). In the 8-year follow-up study published by Strate *et al*^[68] in 2005, both procedures showed equivalent mortality, pain relief, exocrine/endocrine insufficiency, rate of reintervention and quality of life. Similarly, a study by Keck *et al*^[47] including 92 patients showed a trend toward better pain control but similar pancreatic insufficiency rates and weight gain after the Frey procedure when compared to the Beger procedure.

In conclusion, because of its hybrid nature, combining both resection and drainage, the Frey procedure has been conceptualized based on the pathophysiology of chronic pancreatitis. The short and long-term outcome, especially pain relief and quality of life, are better after the Frey procedure than after any other surgical procedure performed for chronic pancreatitis.

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