

Analysis of Human Pancreatic Juice in Tests of Pancreatic Function

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Pancreatic function tests are performed to diagnose chronic pancreatitis and to determine the degree of pancreatic insufficiency contributing to malabsorption. Among the pancreatic function tests, direct pancreatic function test such as secretin-CCK test with duodenal intubation is more specific and sensitive than indirect test such as NBT-PABA test and fecal pancreatic enzyme test. Therefore, secretin-CCK test is accepted as gold standard for the diagnosis and functional assessment of chronic pancreatitis.

However, secretin-CCK test with duodenal intubation is relatively difficult to perform because they require gastrointestinal intubation and take time. In addition to difficulty, they allowed little insight into the nature and sequence of normal and pathophysiological events within pancreas because of contamination with biliary, gastric, and duodenal secretion and rapid activation of pancreatic zymogens by intestinal enteropeptidase.

The development and popularity of endoscopic retrograde cannulation of pancreatic duct allows collection of pure pancreatic juice uncontaminated with bile and duodenal secretions. Since Rinderknecht et al. (8) reported profiles of pure pancreatic secretions obtained by direct pancreatic duct cannulation in normal healthy human subject, intraductal secretin-CCK test in which pancreatic juice are obtained, has been reported by several investigators. However, comprehensive comparative studies between the duodenal intubation test and intraductal secretin-CCK test have remained to be done before definitive conclusions can be obtained.

Cotton and coworkers reported pure pancreatic juice study in normal subjects and patients with chronic pancreatitis. They concluded diagnostic role of intraductal

pancreatic function test was limited because there was considerable overlap in all parameter such as volume and bicarbonate and protein concentrations between normal and patients with chronic pancreatitis. However, some other investigators provided promising results. Recently, Ochi et al. (5) reported the clinical usefulness of the intraductal secretin test in order to ascertain whether it can substitute for the conventional duodenal secretin test. It showed that two tests showed comparable inter-individual coefficients of variation, significantly good correlations, and comparable diagnostic efficiencies. This discrepancy might be due to different patient population in terms of severity of chronic pancreatitis and from different test protocol in which dose and kinds of hormone preparation used and test duration were varied. Among these, severity of pancreatitis must be accounted for interpretation and/or design of experiments because pathological extents of chronic pancreatitis showed wide spectrum. The earliest changes occur in the branch ducts and consist of ectasia and narrowing caused by obstruction. As disease progresses, the branch ducts increasingly dilate. This is accompanied by dilatation and/or stenosis of main ducts. In advanced stages, both the main duct and branched ducts become more abnormal. Ultimately, the main pancreatic duct either appears as a "chain-of-lake" or is uniformly wide dilated. This morphological derangement can be showed by endoscopic retrograde pancreatogram and classified by Cambridge classification I to III. However, functionally, there is a very large reservoir of pancreatic exocrine function. More than 90% of the pancreas must be damaged before maldigestion of fat and protein is manifested. Even the secretin stimulating test is probably abnormal only when more than 60 percent of exocrine function has been lost.

For clarifying correlation of loss of pancreatic exocrine function and morphologic derangement and determining when is optimal test time and which biochemical parameters are required for better discrimination of normal and chronic pancreatitis, we performed secretin-CCK stimulating intraductal secretion test in normal healthy person and patients with chronic pancreatitis. Ten healthy normal volunteers and 30 chronic pancreatitis patients (Cambridge class I 5cases, II 13 cases, III 12 cases) were subject to study. Pure pancreatic juice were obtained by endoscopic pancreatic duct cannulation with gentle aspiration. Secretin (0.25 cu/kg) and CCK (40

Key Words: Pancreatic Exocrine Function; Pancreatic juice; Chronic Pancreatitis

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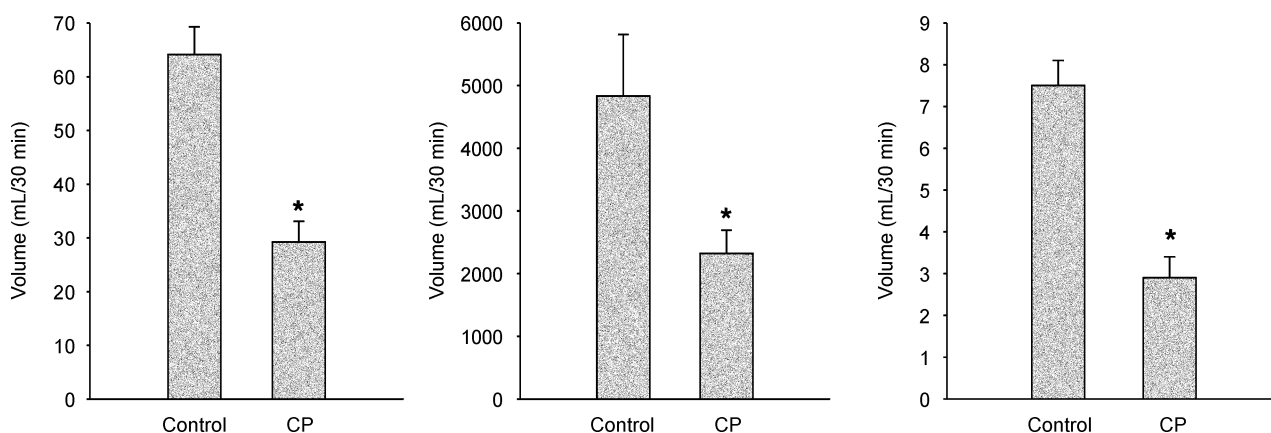


Fig. 1. Pancreatic exocrine secretory response in chronic pancreatitis. Pancreatic exocrine secretion including volume, bicarbonate and amylase output are decreased in patients with chronic pancreatitis (CP) compared with that of normal subjects. * $p < 0.05$ vs. normal

ng/kg) were intravenously bolus injection. Pancreatic juice were collected for 30 min in 5 min aliquots. Volume, bicarbonate, amylase and protein outputs were measured. Lower limit value were calculated by equation (mean value $-1.5 \times$ S.D). In this study, pancreatic exocrine secretion including volume, bicarbonate and amylase outputs were decreased in patients with chronic pancreatitis compared with that of normal persons (Fig. 1). Although magnitudes of impairment in exocrine functions are well correlated with morphologic classification in chronic pancreatitis, parameters of pancreatic exocrine function are not statistically significant in mild chronic pancreatitis such as Cambridge I in ERP (Fig. 2). This result concurs with result of Wada et al. (4). They reported that there was no significant difference in any parameters between normal and Cambridge I and II. It means pancreatic exocrine function test even by intra-

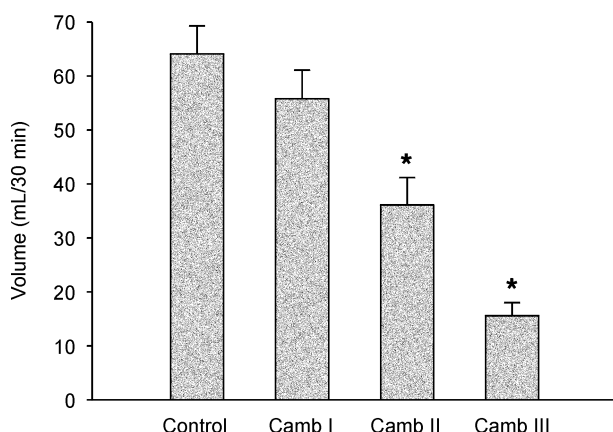


Fig. 2. Pancreatic volume secretion according to Cambridge classification in chronic pancreatitis. Pancreatic volume output is significantly decreased in patients with Cambridge II and III ductal changes compared with that of normal subjects. * $p < 0.05$ vs. normal

ductal secretin-CCK test has a limitation in diagnosing mild pancreatitis. Also, it is important point to consider when previous reports about pancreatic function test was reviewed because subjects were not precisely classified in reports of Denyer et al. (7) and Ochi et al. (5).

Another concerns about intraductal secretin-CCK test are what is useful parameters and minimal duration of test for discrimination of chronic pancreatitis from normal control. We analyzed four parameters, volume, bicarbonate output, amylase output and protein output. Among the four parameters, bicarbonate output and secretory volume are useful for evaluating chronic pancreatitis because protein and amylase output shows wide inter-individual variation. This finding concurs with Ochi and co-workers' finding. In Wada et al. (4) report, however, no significant difference was found in secretory volume, amylase output, and bicarbonate output. They explained this result was due to loss of part of the secretion flowing out through the duodenal minor papilla and/or between the catheter and main pancreatic duct wall. However, considering methods of pancreatic juice collection by syringe with mild negative pressure, Wada's explanation is not likely.

For determining minimal duration of test, analysis of time response curve would be meaningful. In our study, volume, bicarbonate, amylase and protein outputs were increased at first 5 min and reach peak levels at 10-15 min, after then sustained plateaus (Fig. 3). It means 15 min collection of pancreatic juice is enough for test.

From analyzing data of normal individual, the normal value of volume and bicarbonate output in 15 min PPJ sample are 5.6 mL and 6.3 mEq. The sensitivity and specificity of volume in 15 min sample are 61.9% and 100%. The sensitivity and specificity of bicarbonate in 15 min sample are 76.2% and 100%. This finding concurs with previous findings of Ochi et al. (5). In Ochi

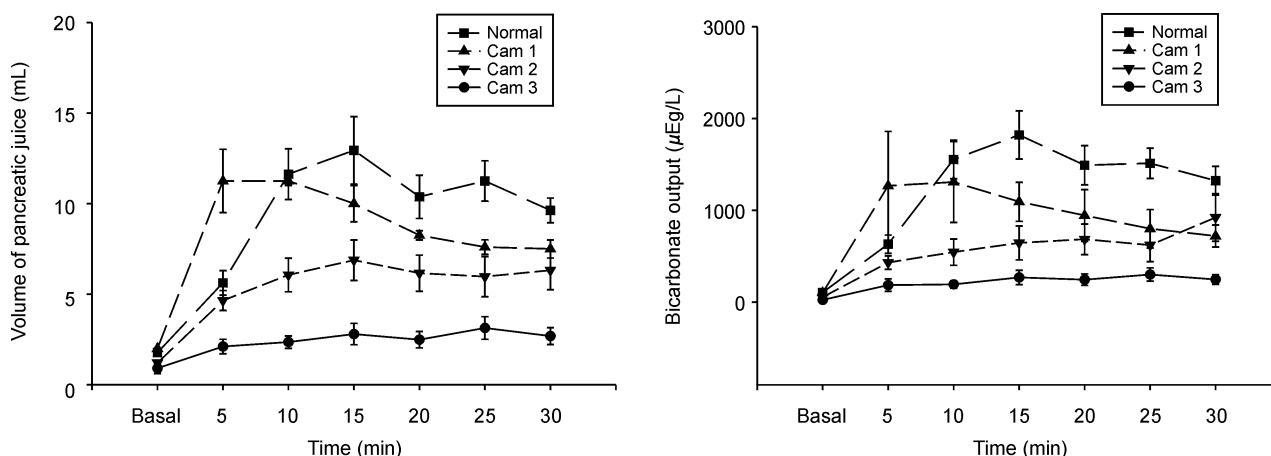


Fig. 3. Bicarbonate output and secretory volume response curve in secretin-CCK stimulating pancreatic exocrine function test by collecting pure pancreatic juice. Bicarbonate output and volume are increased at first 5 min and reach peak levels at 10-15 min, after then sustained plateaus. Magnitudes of impairment in exocrine functions are well correlated with morphologic classification in chronic pancreatitis while parameters of pancreatic exocrine function are not statistically significant in mild chronic pancreatitis such as Cambridge I in ERP.

and co-workers' results, the 10 min secretory volume and 10-min bicarbonate output during 20-min juice collection after stimulation with bolus intravenous infusion of secretin were suggested to be most sensitive parameters showing a sensitivity of 69.2% for secretory volume and 61.5% for bicarbonate output. Although the procedure requires an experience investigator, collecting pancreatic juice samples by endoscopic cannulation does not require a gastrointestinal intubation procedure and takes a shorter time than collecting duodenal juice by the duodenal intubation method.

In addition to pancreatic function test, collecting pure pancreatic juice by endoscopic cannulation is useful for other purposes such as studying exocrine function and detecting gene mutation in pancreatic cancer. Recently several investigators reported usefulness of detecting K-ras mutation in pancreatic juice for detecting early pancreatic cancer.

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