Effects of cholecystectomy on the changes of motility of Beagle dogs' sphincter of Oddi[1]

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ABSTRACT

PURPOSE: To observe the effect of cholecystectomy on the changes of motion pattern of Beagle dogs' sphincter of Oddi (SO), and investigate the modulatory role of nitric oxide (NO) and cholecystokinin (CCK) in the regulation of SO.

METHODS: Pressure of common bile duct, SO motility, response to bolus injections of cholecystokinin (CCK, 20 ng/kg and 100 ng/kg), basal pressure (BP) and phasic contraction amplitude (PCA) were measured respectively by manometry in six Beagle dogs before and after cholecystectomy.

RESULTS: After cholecystectomy, the pressure and diameter of common bile ducts (CBD) was significantly increased ($p<0.01$); BP and phasic contraction frequency (PCF) were also increased, however, no significant differences were found between the two groups; the SO motilities was not significantly changed. The relaxation responded to physiological dose of CCK (20ng/kg) was decreased, while bolus-dose of CCK (100ng/kg) induced rapid contractions and decreased PCA after cholecystectomy. The regulation pattern of SO pressure modulated by NO and its inhibitor had changed after cholecystectomy.

CONCLUSION: After cholecystectomy in Beagle dogs, no obviously change of motion pattern of SO was observed through self-compensation, but these compensations may lead to some changes of regulation pattern of CCK and NO on SO.

Key words: Cholecystectomy. Sphincter of Oddi. Nitric Oxide. Cholecystokinin. Dogs.

Introduction

Sphincter of Oddi (SO) is an important neuromuscular complex that regulates the flow of bile and pancreatic juices into the duodenum and diverts hepatic bile into the gallbladder reservoir[1]. Several studies indicate that SO dysfunction, stenosis, and an abnormal motor activity of the SO, usually presents with biliary-like pain and acute pancreatitis after cholecystectomy[2]. However, the mechanism, especially the exact change of SO motility after cholecystectomy, is not clear. Many studies demonstrate that cholecystokinin (CCK) is the most important hormone affecting SO motility[3,4]. The level of CCK determines the extent of SO relaxation and promotes flow of bile and pancreatic juice into the duodenum. In addition, nitric oxide (NO), a well-known mediator of vascular smooth muscle relaxation, has been shown to be an inhibitor of SO activity[5]. The study of Howard S reports that baseline SO phasic activity can be regulated by cholinergic stimulatory and NO-mediated inhibitory (Nω-nitro-L-arginine methyl ester (L-NAME)) neural pathways[6].

Currently, the basal pressure (BP) and phasic contraction amplitude (PCA) are measured by SO manometry[1]. Thus our experiment is established with the manometry system using low-compliance pneumohydraulic capillary infusion. We measured the motion pattern of SO before and after cholecystectomy as well as the response to CCK after cholecystectomy. In addition, the effect of NO on SO activity was evaluated using SNP stimulatory and L-NAME.

Methods

The experimental protocol was reviewed and approved by the Ethics Committee on Animal Experiments of the Medical School of Shanghai Jiaotong University, and the study process was conformed to the Guiding Principles in the Care and Use of Animals.

Twelve healthy adult male Beagle dogs of weighing 10-12 kg, provided by Animal Care and Use Committee of the Medical School of Shanghai Jiaotong University, were randomly divided into control group and cholecystectomy group. The dogs in the control group were sham-operated.

Equipments and reagents

The manometry system was consisted of a low-compliance SO triple-lumen manometry catheter (Lehman SO manometry catheter, Wilson-Cook Medical Inc., Winston-Salem, NC, USA), a low-compliance pneumohydraulic capillary infusion system and a PowerLab multichannel system for recording and processing biological signals. The two lumens of the catheter were perfused with distilled water through low-compliance capillary at a rate of 0.25 ml/min by nitrogen pump under a constant pressure (420-450 mmHg), while the third lumen was preserved for drainage. The pressure transducer was used for receiving the dynamic pressure change from the duple-lumen manometry. PowerLab hardware system (AD Instruments Corporation, Australia) and Chart 5.0 software system were applied to record these signals.

Reagents used in the research including Cholecystokinin-octapeptide sulfate (CCK, C2175), Sodium nitroprusside dehydrate (SNP, 71788) and N_{ω}-Nitro-L-arginine methyl ester hydrochloride (L-NAME, N5751) which could inhibit nitric oxide synthetase (NOS), were all purchased from Sigma-Aldrich Corporation.

Experimental protocol

The cholecystectomy group received standard cholecystectomy after fasting more than 12 hours and then anesthesiaed with intramuscular pentobarbital. All the dogs were fed properly for three months and accepted an upper midline laparotomy followed by an incision about 3-5 centimeters below the pylorus, on the opposite side of mesoduodenum. Then manometry catheter was inserted into common bile ducts (CBD) and SO retrogradely through duodenal ampulla to record CBD pressure, SO motility and their response to different doses injections of drugs. Femoral veins, dissected from Beagle dogs, were dissected for injection of CCK (20ng/kg, 100ng/kg) and L-NAME (10mg/kg), while CBD were isolated for continuous instilling SNP (10μg/kg/min). The effect of nitric oxide (NO) and nitric oxide inhibition (NOI) on the SO of the cholecystectomy group was evaluated using instilling SNP to imitate the effect of nitric oxide and injecting L-NAME to inhibit the synthesis of nitric oxide synthase (NOS). All the dogs were killed by intracardiac air injection and the corpses were disposed properly.

Data acquisition and analysis

The pressure measured at the level of duodenal papilla was set as zero. After recording the CBD pressure for 60 seconds stably with the drainage lumen closed, the catheter was pulled to the level of SO by a station-pull-through technique. Once two pressure sensors accepted the pressure wave of SO phasic contractions simultaneously, we fixed the catheter and opened the drainage lumen to record the motion of SO for about two hours. After injection, the computer

would record the changes for at least ten minutes.

The variables of SO motility included basal pressure (BP), phasic contraction amplitude (PCA) and phasic contraction frequency (PCF). BP was defined as the minimal pressure between two adjacent SO phasic contractions. PCA was defined as the value from the basal pressure to the peak of the phasic contraction. PCF was defined as the numbers of the phasic contraction per minute. We divided each cycle of SO's motion into 20 equal intervals and calculated the data with every 5 % as one unit. The medicament effect was estimated on the percentage of post-injection and pre-injection value.

Statistical analysis

All data were described as mean ± SD and statistical analysis was performed using SPSS 17.0 software. The difference between two groups was analyzed by Student's t-test. The statistical significance of differences between three or more groups was analyzed by ANOVA. $p<0.05$ was considered to be statistically significant.

Results

CBD pressure

The pressure of CBD was 14.42±3.89mmHg after cholecystectomy, significantly higher than 5.39±2.37mmHg measured before cholecystectomy ($t=4.858$, $p<0.01$). Furthermore, the diameter of CBD of dogs in cholecystectomy group was wider than that of the control group by visual observation with the naked eyes.

Cyclic motion of SO

Before and after cholecystectomy, the motion of SO showed a same cyclic pattern of gradual increasing and recovery (Figure 1).

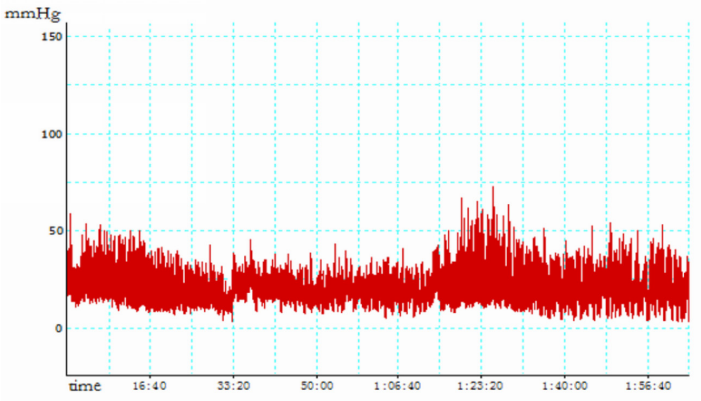

FIGURE 1 - The cyclic motion of sphincter of Oddi.

BP, PCF and PCA presented a phasic process (Figure 2A, B, C).

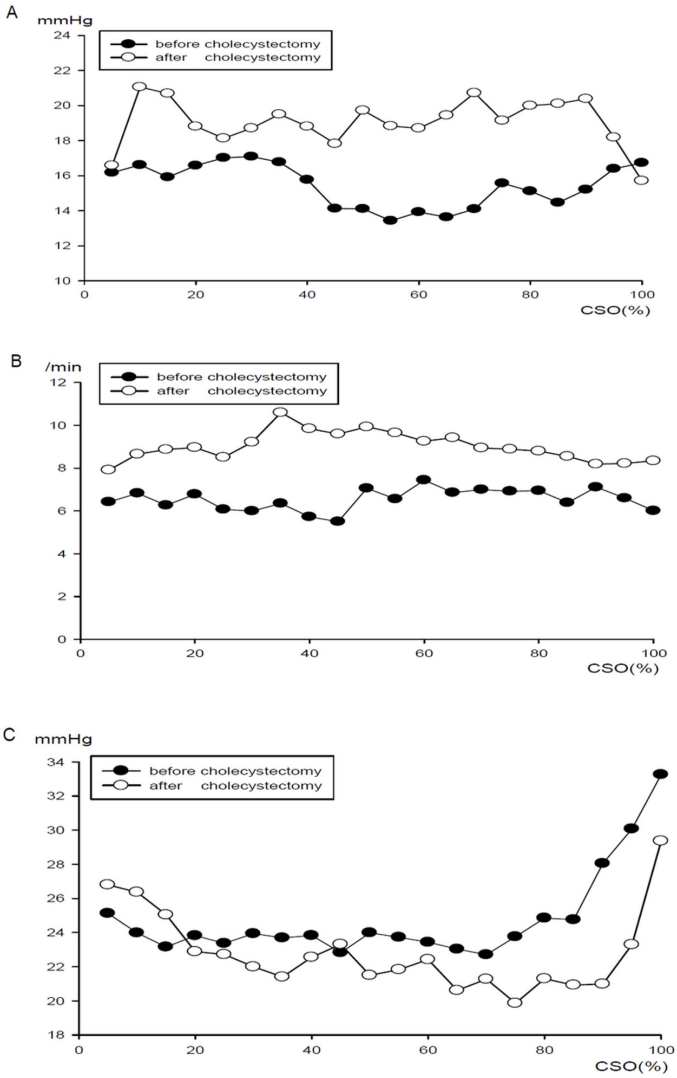

FIGURE 2 - Motility of sphincter of Oddi in one cycle before and after cholecystectomy. A. Change of BP in one cycle; B. Chang of PCF in one cycle; C. Change of PCA in one cycle.

After cholecystectomy, BP and PCF was increased by many units (Figure 2A, B), however, no significant differences were found in the average and peak values of the whole period of motion between the two groups (Table 1).

TABLE 1 - The characteristics of SO motility before and after cholecystectomy.

Variables of SO motility		BP (mmHg)	PCF （/min）	PCA （mmHg）
Average value	Before operation	15.44±3.64	6.53±2.83	24.77±5.54
	After operation	19.06±5.46	9.01±4.21	22.83±6.82
Maximum value	Before operation	21.16±5.84	8.83±3.11	33.53±5.27
	After operation	26.10±9.04	11.52±5.15	29.37±6.78

Results were expressed as mean±standard deviation (SD). BP, basal pressure; PCF, phasic contraction frequency; PCA, phasic contraction amplitude. $p<0.05$, the difference was regarded as significant, but whether average value or maximum value did not change significantly after cholecystectomy.

Effect of physiological dose of CCK (20ng/kg): Compared with the average value of the normal cycle, BP and PCA were inhibited effectively by physiological dose of CCK several minutes after injection in the control group. However, the effect of suppression of BP and PCA disappeared or was weakened in the cholecystectomy group (Table 2).

TABLE 2 - Response of BP and PCA to CCK (20ng/kg) before and after cholecystectomy (mmHg).

Variables of SO motility	Before injection	1 minute	2 minutes	3 minutes	10 minutes
BP(before operation)	15.44 ± 3.64	10.46± 4.30*	9.47 ± 3.75*	11.66 ± 3.71*	16.28 ± 4.44
BP(after operation)	19.06 ± 5.46	20.77 ± 11.90	21.75 ± 9.98	21.63 ± 8.88	21.64 ± 8.16
PCA(before operation)	24.77 ± 5.54	17.34 ± 5.14*	15.01 ± 4.15*	18.92 ± 6.56*	27.00 ± 4.90
PCA(after operation)	22.83 ± 6.82	16.31 ± 7.40*	18.55 ± 7.63*	20.12 ± 7.09	22.49 ± 7.61

Results were expressed as mean±standard deviation (SD) and tested by analysis of variance and LSD. Before injection, mean value within the thirty minutes before bolus injection; 1 minute, mean value within the first 1 minute after injection; 2 minutes, mean value within the first 2 minutes after injection; 3 minutes, mean value of the first 3 minutes after injection; 10 minutes, mean value of all the 10 minutes recorded after injection. * $p<0.05$, BP and PCA decreased by physiological dose of CCK in at least 3 minutes after injection in the control group, while this suppression was no longer so significant in the test group.

Effect of bolus-dose of CCK (100ng/kg): A mega dose injection increased BP of normal SO in a short time, and PCA was increased more remarkably. However, we detected an inhibition of PCA shortly after injection in dogs accepted cholecystectomy, instead of excitement in the control dogs (Table 3).

TABLE 3 - Response of BP and PCA to CCK (100ng/kg) before and after cholecystectomy (mmHg).

Variables of SO motility	Before injection	1 minute	2 minutes	3 minutes	10 minutes
BP(before operation)	15.44 ± 3.64	18.98 ± 5.78*	20.00 ± 6.42*	16.89 ± 5.08	17.26 ± 4.91
BP(after operation)	19.06 ± 5.46	18.52 ± 9.43	19.91 ± 9.03	20.32 ± 8.19	20.59 ± 5.91
PCA(before operation)	24.77 ± 5.54	39.35 ± 12.28*	43.95 ± 10.83*	35.50 ± 6.65*	27.09 ± 4.79
PCA(after operation)	22.83 ± 6.82	15.04 ± 6.26*	17.05 ± 6.75*	18.24 ± 6.84	20.70 ± 8.16

Results were expressed as mean±standard deviation (SD) and tested by analysis of variance and LSD. *$p<0.05$, mega dose of CCK could increase BP of normal SO in a short time, and PCA more significantly. However, this appearance disappeared, and an abnormal inhibition of PCA could be detected shortly after injection in dogs accepted cholecystectomy.

Effect ratio of physiological dose and bolus-dose of CCK: Figures 3 and 4 described the effect percentage (%) of dosages of CCK injection were varied with time. An unabiding excitement of SO motion between the inhibition and recovery period after injection of CCK (20ng/kg) was observed in the control group, while this tendency was not conspicuous in cholecystectomy group. After the bolus injections of 100 ng/kg of CCK, the motion mode of physiological dose of CCK was recovered after a rapid and intense contraction in the control group. On the contrary, there was a pure suppression effect of SO in the cholecystectomy group (Figures 3 and 4).

Whatever, all variables returned to normal ranges after six to seven minutes injection.

Effect of NO and NOI on the SO: As was shown in Table 4, NO decreased PCA and increased BP mildly (Table 4).

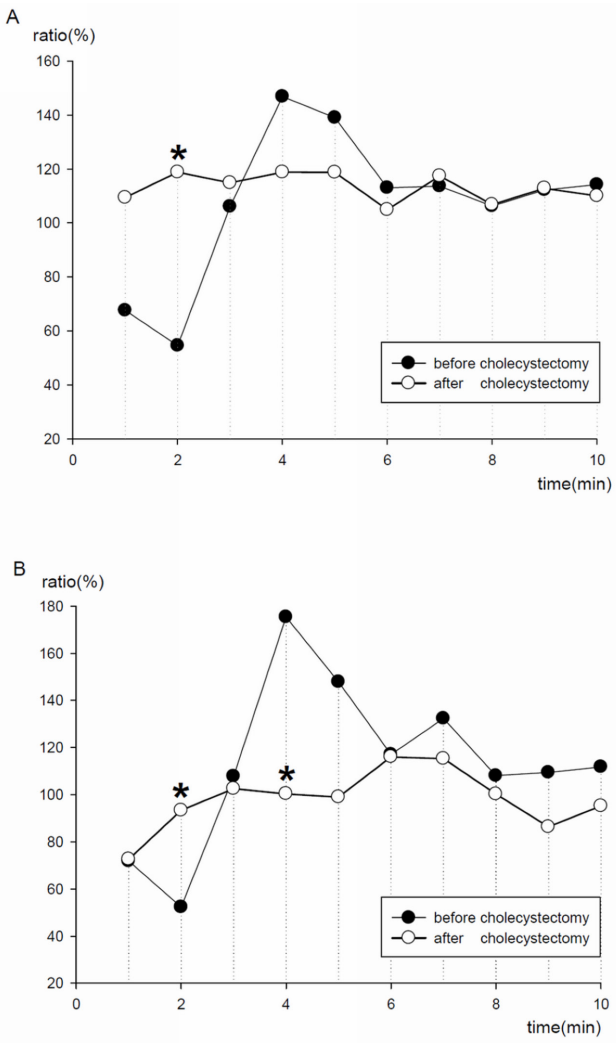

FIGURE 3 - Effect of physiological dose of CCK on SO motility before and after cholecystectomy: injection of CCK (20ng/kg) could significantly inhibit the motion of SO in the first 3 minutes in the control group, following an unabiding excitement. While this situation changed in some key time points as asterisked in the cholecystectomy group, on the basis of independent-samples T test. (t_{3a}=5.207, p=0.000. t_{3b}=2.803; 2.285, p=0.019; 0.045). **A.** The effect of CCK (20ng/kg) on the change of BP; **B.** The effect of CCK (20ng/kg) on the change of PCA.

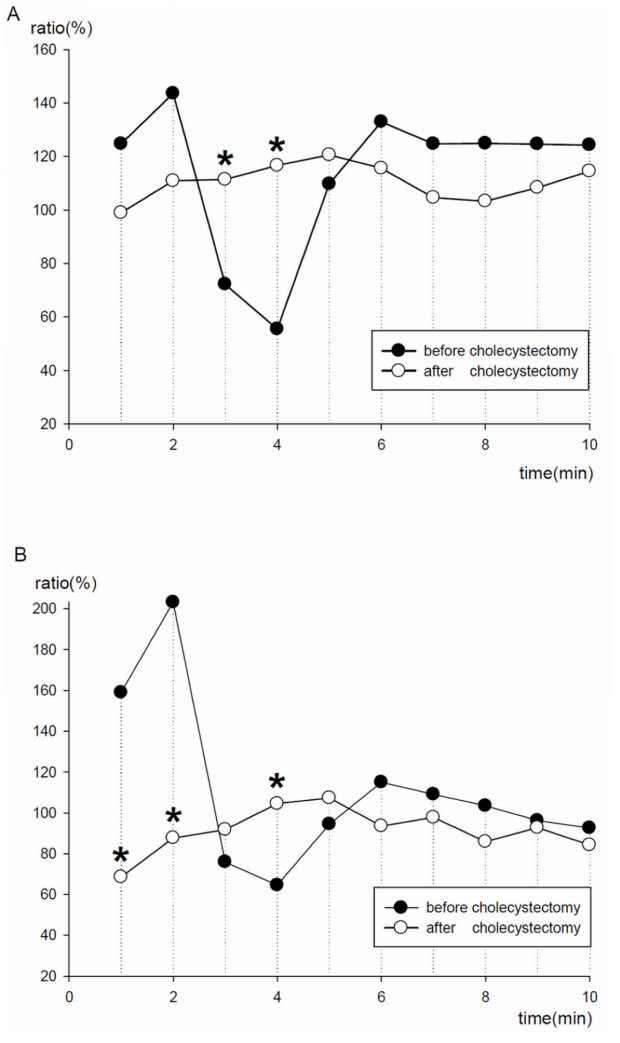

FIGURE 4 - Effect of pharmaco-dose of CCK on SO motility before and after cholecystectomy: a rapid and intense contraction could be detected after an injection of CCK (100ng/kg) in the control group, before returning to the motion mode of physiological dose. On the contrary, there was a pure suppression effect of SO in the cholecystectomy group, as described by asterisks in the figures above. (t_{4a}=2.384; 6.249, P=0.038; 0.000. t_{4b}=4.924; 3.526; 2.384, P=0.001; 0.005; 0.038). A. The effect of CCK (100ng/kg) on the change of BP; B. The effect of CCK (100ng/kg) on the change of PCA.

TABLE 4 – Response of BP and PCA to NO and NOI after cholecystectomy (mmHg).

Group	1 minute		2 minutes		3 minutes		10 minutes	
	BP	PCA	BP	PCA	BP	PCA	BP	PCA
Normal	20.53 ± 4.60	22.69±7.61	20.53±4.60	22.69±7.61	20.53±4.60	22.69±7.61	20.53±4.60	22.69±7.61
NO	22.90 ± 3.31	15.27±7.48*	22.79±2.65	16.17±7.51*	23.26±3.06	17.79±7.55	25.25±5.32*	21.32±10.05
NO+CCK(100)	21.30 ±7.45	13.79±6.81*	22.21±6.48	15.26±6.85*	23.55±6.02	17.18±5.89	24.46±3.74*	20.36±4.63
NO+CCK(20)	22.53±5.58	16.91±4.78	24.15±5.20	18.07±5.31	25.03±4.80*	19.91±6.22	26.03±4.57*	22.03±7.32
NOI	23.01±4.93	15.42±5.01	21.52±4.66	16.37±5.82	20.84±4.77	16.10±5.40	22.92±3.87	16.39±5.96
NOI+CCK(20)	27.01±4.16*	20.03±3.82	26.62±3.37*#	19.07±5.09	26.59±2.03*#	17.96±5.14	26.83±1.61*	16.95±5.97

Results were expressed as mean±standard deviation(SD) and tested by analysis of variance and LSD. Normal, mean value before bolus injection; NO, mean value after instilling SNP to imitate the effect of nitric oxide; NO+CCK, mean value after instilling SNP and injecting CCK at the same time; NOI, mean value after injecting L-NAME to inhibit the synthesis of nitric oxide synthase; NOI+CCK (20), mean value after injecting NOI and CCK at the same time. * P<0.05(compare with "Normal"), NO could still decrease PCA, but the addition of physiological dose of CCK couldn't relax the SO furthermore. As well as the inhibitory effect of CCK (100ng/kg) in the test group (Table 3), the combined apply of NO and CCK (100ng/kg) would reduce PCA more obviously. # P<0.05(compare with "NOI"), different from previous relevant studies in normal dogs, L-NAME couldn't increase the motility of SO obviously in cholecystectomy group, excepted for the join of CCK (20ng/kg).

The sphincter tension was markedly increased in the control group due to L-NAME, while motility of SO didn't change obviously in the cholecystectomy group. Combined application of SNP and physiological doses of CCK could not relax the SO. After the operation of combined application of SNP and bolus dose of CCK (100ng/kg), the PCA decreased in the cholecystectomy group, while the SO was excited in the control group. However, combined application of L-NAME and physiological doses of CCK, the BP of SO increased to a certain extent at least ten minutes after injection (Figure 5).

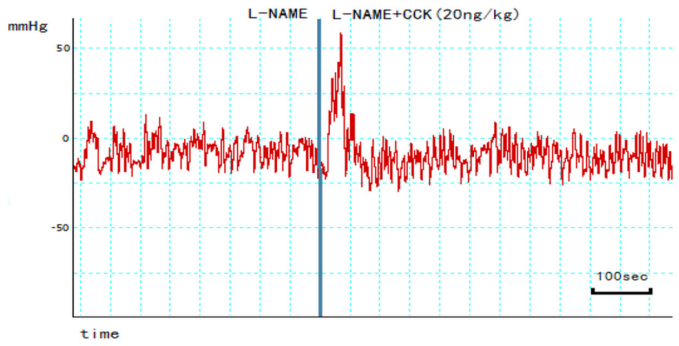

FIGURE 5 - Effect of L-NAME and combining with physiological dose of CCK on SO motility after cholecystectomy: when L-NAME seemed to lose the excitatory effect after operation, the addition of CCK (20ng/kg) inconceivably increased the motion of SO at least in ten minutes after injection.

Discussion

The regulation of sphincter of Oddi includes three aspects: neuroregulation, hormonal regulation and local regulation. Neuroregulation[7] can be grouped into intrinsic and extrinsic neural regulation. Intrinsic innervations mainly include cholinergic neurone, adrenergic neurone and non-adrenergic-non-cholinergic neurone (NANC)[8], while extrinsic innervations contain sympathetic fibers from celiac ganglia and parasympathetic fibers from vagus nerve[9]. The motility of the SO can be influenced by a variety of gastrointestinal hormones and such as CCK, gastrin, somatostatin and secretin. Among them, CCK is the most prominent hormone affecting SO motility. However, the local regulation between gallbladder and SO is unclear. Only few studies indicate rise pressure of gallbladder and CBD lead to decrease of SO pressure[10]. Some researchers presume that postcholecystectomy syndrome (PCS)[11], which can be diagnosed by manometry, occurs because of losing this coordination after cholecystectomy.

In this study, we found that BP and PCF are slightly higher, but no statistical significant difference was observed in every unit after cholecystectomy ($p<0.05$). However, the diameter and pressure of CBD and volume of SO were increased, which demonstrated that SO strive to adapt to the changes of biliary dynamics after operation. Thus, SO could adjust to the changes produced by cholecystectomy because of internal compensation. Losing the tension bumper, such as gallbladder, aggravate the exhaustion of biliary dynamics and motility of SO which would lead to unexplained abdominal pain sometime after cholecystectomy. In fact, the appellation of PCS has been replaced gradually by sphincter of Oddi dysfunction (SOD)[12], because some patients suffering from stomach and intestinal disorders, peptic ulcer and cholelithiasis, who haven't accepted any operation, could present the similar symptoms[13] and manometry characteristics. Some studies report that only 14% of unknown abdominal pain after cholecystectomy could be ascribed to SOD[14], excluding the possibility of biliary leak, biliary stricture, cystic duct remnant, bile duct injury.

The SO motility during the interdigestive phase is closely correlated to the migrating motor complex (MMC) of the duodenum which can promote bile flowing into the gallbladder. The four SO phases of A, B, C and D correspond to the four phases of duodenum MMC I, II, III and IV, respectively. In addition, CCK is an important hormones that are responsible for SO relaxation and gallbladder contraction during the digestive phase.

In this study, the response of SO motility to CCK before and after cholecystectomy in Beagle dogs was also evaluated. In control group, physiological dose of CCK (20 ng/kg) leaded to inhibition of SO rapidly, sequentially to the excitement and recovery period, while bolus-dose of CCK (100 ng/kg) could arouse intense contractions by combining submucosal CCK receptors. Thus, SO motility showed an inhibition–excitement–recovery pattern after injections of physiological dose of CCK, and an excitement–inhibition–excitement–recovery pattern after injections of bolus-dose of CCK. In cholecystectomy group, the response of physiological dose of CCK was weakened sharply, except a residual short suppression of PCA, while bolus-dose of CCK resulted in abnormal inhibitory action, instead of the rapid contractions. The compensation for cholecystectomy includes an increased concentration of CCK in vivo and a reduced sensitivity of receptors to CCK was speculated, and the physiological dose of CCK had lost the effect of suppression. Thus, the compensation could remove the excitement produced by the binding of CCK to its receptor in the sphincteric mucosa, and required a larger dose of CCK for relaxation.

It has been reported that NO, as one of the most important neurotransmitters of non-adrenergic-non-cholinergic neurone (NANC)[15,16], can inhibit the motion of SO[17,18] and induce

the relaxation produced by CCK[19]. However, the effect of NO in patients or animals after cholecystectomy is not clear. In our study we find that NO significant inhibited SO activity before cholecystectomy, while NO could no longer decrease the basal pressure (BP) after operation, though some effect of decreasing phasic contraction amplitude (PCA) was reserved. Moreover, the intense contractions caused by L-NAME which was a kind of inhibitor of nitric oxide synthetase (NOS)[20], disappeared in cholecystectomy group. We also occasionally find the combined application of L-NAME and CCK (20ng/kg) could enhance the motion of SO in a period. We conjectured that contractibility of excised SO of animals which have underwent cholecystectomy or cystic duct ligation was heightened, then the NOS amount was greatly increased for compensation in mucous layer and smooth muscle layer, which results in a reduced effect for the original dose of L-NAME. However, the active motion caused by the addition of CCK (20ng/kg) to L-NAME was hard to understand. We conjectured that the active motion might be aroused by CCK itself, or L-NAME blocked the relaxation pathways of CCK induced by NO, just as reported in our previous studies.

Initial studies demonstrated that the SO is sensitive to all narcotics and bile duct pressure is increased. All narcotics increase SO phasic wave frequency and interfere with SO peristalsis. Thus, in order to reduce the effect of narcotics on SO, low-dose *i.m.*pentobarbital (5%, 1 mL/kg) was used for operation.

In summary, no significant changes of motion of SO was observed during fasting in a period of three months after cholecystectomy, however, the effect of CCK and NO were different from before cholecystectomy, due to the adaptation of SO after operation. Moreover, we inferred that resecting an ill gallbladder is a positive surgery, which could be beneficial to the organism. In addition, the view of removal of calculus and preservation of gallbladder was not supported, because of the recurrence of stones and favorable compensation of SO itself.

Conclusion

After cholecystectomy in Beagle dogs, no obviously change of motion pattern of sphincter of Oddi was observed through self-compensation, but these compensations may lead to some changes of regulation pattern of cholecystokinin and nitric oxide on sphincter of Oddi.

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