En bloc thoracic duct ligation and subtotal pericardectomy in dogs and cats with idiopathic chylothorax by thoracotomy versus thoracoscopy in 20 cases (2005-2013)

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Abstract

Chylothorax is a devastating disease in dogs and cats. A golden standard for treatment of idiopathic chylothorax has not been described yet. Goals for this study were to evaluate en bloc TDL and SP as a treatment for idiopathic chylothorax and to compare outcomes of treatment by thoracotomy and thoracoscopy. 16 dogs and 4 cats with idiopathic chylothorax, that were surgically treated between 2005 and 2013 at the Faculty of Veterinary Medicine Utrecht, were studied retrospectively. In 15 patients thoracotomy was performed during surgery, the other 5 were operated thoracoscopically. All patients had en bloc TDL performed in combination with SP, except for 3 dogs that were treated with en bloc TDL only. Overall 9 out of 17 patients (53%) became disease free. Success for thoracotomy was 50% and 60% for thoracoscopy, this difference turned out to be not significant. For patients treated with both en bloc TDL and SP success was 47%. In this group thoracotomy only had successful outcomes in 40% of patients, which is also not significantly different from the 60% success with thoracoscopy. The mean survival time for both treatment techniques was also similar. Together with decreased hospitalization time, post-operative pain and morbidity previously reported for the less invasive thoracoscopy, this treatment technique might be preferred over the classic thoracotomy. The success rate for the combined treatment with TDL and SP was, for unknown reason, lower than expected. Despite this outcome the combination of en bloc TDL and SP is still considered to be a good treatment option for idiopathic chylothorax. Further research for new lymph drainage routes formed after en bloc TDL and for the role of high venous pressure and SP on lymph drainage is needed. Moreover gaining more understanding about the etiology of idiopathic chylothorax and persistent nonchylous effusion after treatment should be subjects of ongoing study.

Introduction

Chylothorax is an uncommon condition, veterinary seen in dogs and cats, which is difficult to treat and can have devastating effects. Due to the accumulation of chyle in the pleural space this disease causes mainly respiratory problems. Chyle is a milky lymph fluid produced by the intestinal lacteals, that mainly absorb fat during digestion. It therefore has a high concentration chylomicrons, lipoprotein molecules that mostly consist of triglycerides but also contain cholesterol, phospholipids and proteins.(Allman et al. 2010; Fossum et al. 2004; Singh 2012b) The chyle containing lymph is transported to the cisterna chyli in the craniodorsal abdomen, which is the lymphatic reservoir for lymph produced in the caudal body. From there the fluid flow continues through the thoracic duct (TD), the largest lymph vessel in the body. The TD is located in the mediastinum, dorsal to the aorta and ventral to the thoracic vertebrae, and empties its content into the venous system at level of the jugoclaval angle. (Singh 2012b; Staiger, Stanley, and McAnulty 2011) Chylothorax develops when chyle leaks from the thoracic duct into the pleural space. The chyle leaks through enlarged dilated lymph vessels,

lymphangiectasia, caused by increased lymph production, obstruction of lymph drainage or both. There have been described multiple causes for chylothorax, including cardiac diseases, cranial mediastinal masses, thrombosis of the cranial vena cava, congenital abnormalities of the thoracic duct, trauma of the thoracic duct, diaphragmatic hernia, lung lobe torsion, fungal granulomas and heartworm disease. (Carobbi, White, and Romanelli 2008; da Silva and Monnet 2011; Fossum et al. 2004; McAnulty 2011; Singh 2012b; Stewart 2010; Viehoff and Stokhof 2003)

When an underlying cause is found, treatment should be focused on eliminating the primary problem. However, often none of these causes can be found, the chylothorax is then considered to be idiopathic. The chyle leak is then probably also caused by formation of lymphangiectasia, but for unknown reasons. (McAnulty 2011; Viehoff and Stokhof 2003) Treatment of idiopathic chylothorax is controversial and so far there has not been described a golden standard yet. Curative treatment is necessary because chyle is an irritant that can cause severe pleuritis and pericarditis. Furthermore chronic chylothorax can result in hypo-proteinemia, immunodeficiency, dehydration and weight loss. Therefore several different medical and surgical treatments have been proposed. Medical treatment consists of a low fat diet, administration of rutin and intermittent palliative thoracocentesis. Unfortunately this form of treatment is not very successful on long term in most cases. For surgical treatments higher success rates are reported. Different procedures that have been described are ligation of the thoracic duct (TDL), subtotal pericardectomy (SP), cisterna chyli ablation (CCA), pleurodesis, thoracic omentalization, pleurovenous shunting and combinations of these techniques.(da Silva and Monnet 2011; Fossum et al. 2004; Mayhew et al. 2012; Singh 2012a) Although most experts do advocate preforming at least ligation of the thoracic duct, the search for the best treatment still continues due to small research groups and variable study outcomes. Some available surgical treatments can be performed via both classic open thoracotomy and modern less invasive thoracoscopy. In human treatment thoracoscopy is preferred because it is associated with less postoperative pain, decreased patient morbidity and shorter hospitalization.(Allman et al. 2010; Lyon et al. 2013; Radlinsky et al. 2002) When the thoracic status of the patient turns out to be unsuitable for the thoracoscopic procedure, for example when severe thickened pleura unable good vision on the needed structures or when significant hemorrhage occurs, the surgery still has to be converted to thoracotomy. The need for conversion is rarely reported in veterinary literature. (Lyon et al. 2013; Radlinsky 2009) At this moment thoracoscopy seems technically possible but there only are a few veterinary reports about treatment of chylothorax with those minimally invasive procedures and their possible advantages or disadvantages. There are, however, signs for thoracoscopy causing less postoperative pain and analgesia requirement, shorter surgery and recovery time and less respiratory compromise than after thoracotomy.(Leasure et al. 2011; Radlinsky et al. 2002; Radlinsky 2009; Walsh et al. 1999) Thereby similar success rates as for the same procedure with thoracotomy have already been claimed. (Allman et al. 2010; Mayhew et al. 2012)

The goal of this study was to retrospectively evaluate the results of surgical treatment for idiopathic chylothorax by en bloc TDL combined with SP, using 2 different surgical techniques: open thoracotomy versus noninvasive thoracoscopy. Thereby, a question was whether the success after thoracoscopic treatment is similar to the outcome for thoracotomy surgery. Based on previously published literature a similar success rate of 57-100%,(Allman et al. 2010; Bussadori et al. 2011; Carobbi, White, and Romanelli 2008; Fossum et al. 2004; Mayhew et al. 2012; McAnulty 2011) is indeed expected after both techniques. When this expectation is correct, thoracoscopic treatment might be the better option due to its less invasive character.

Materials and methods

Case selection

In this retrospective study patient dossiers from all animals diagnosed with idiopathic chylothorax that underwent surgical treatment between January 2005 and March 2013 in the University Clinic for Companion Animals at the

Faculty of Veterinary Medicine Utrecht (FVMU) were used. The diagnosis of chylothorax was confirmed when the triglyceride concentration of the pleural fluid exceeded the triglyceride content of blood serum. When with further medical examination and imaging of the thorax no obvious cause of chylothorax was discovered it was considered idiopathic.

Data collection

Before reading the case files, a list with information of interest was established on guidance of literature. Information that was searched for in the dossiers included signalment, history, findings in physical examination, findings in respiratory examination, results of blood tests, results of thoracic fluid tests, cytology, results of radiography and computed tomography, echocardiographic findings, surgical procedure, surgeon, operation time, pathology, special findings or complications during surgery, post-operative recovery and analgesia, final duration of hospitalization, outcome, survival time and cause of death.

Surgery

Patients were either treated by thoracotomy or thoracoscopy. All patients underwent en bloc ligation of the thoracic duct. The technique used for en bloc ligation in thoracotomy was described by Viehoff and Stokhof published in 2003.(Viehoff and Stokhof 2003) Additional subtotal pericardectomy was performed in most cases. In patients treated via thoracoscopy en bloc TDL was done by either coagulation of the tissue by the LigaSure[a] or by clipping the tissue with endoclips or ligaclips. Additionally the patient was rotated from ventral to dorsal recumbency and a pericardial window was made. After surgery a thorax drain was placed, patients were hospitalized as long as the drain was substantial productive and needed to stay in place.

Follow-up

Follow-up was performed at the end of October 2013, by telephonic contact with the patients owners. Owners were asked whether the patient was still alive, and if not, whether the cause of death was related to the presence of chylothorax or liquothorax and what date the animal passed away. Furthermore they were asked if the patient showed signs of recurrent or persistent chylothorax or liquothorax after surgery, if the patient is or has been on conservative therapy (low fat diet, thoracocentesis and use of rutin) for chylothorax after surgery, how the patient has recovered after surgery and if the patient has had other medical problems since surgery. When telephonic contact could not be established, a questionnaire with the same questions was sent by mail.

Patients were considered disease free when no clinical signs of chylothorax or liquothorax were present. When signs continued after leaving the clinic or reoccurred within one month after surgery this was considered a persistent chylothorax or liquothorax. Patients with symptoms that returned later on were defined to have recurrent disease.

Statistical analysis

For most data descriptive statistics were performed, the outcomes were given in mean ± standard deviation. To describe the long term follow-up Kaplan Meier survival analysis was done with SPSS. Patients were censored when lost in follow-up, when died due to causes unrelated to chylothorax and when still alive on time of last follow-up. Mean survival time from time of surgery was calculated for all patients as well as for both the thoracoscopy and thoracotomy treatment groups. Significance between success percentages of different groups was determined with the Chi-squared test.

Results

patients

20 patients, 4 cats and 16 dogs, were included in this study, see Table 1 and 2. All four cats were castrated males and domestic short hairs. The cats were 13 years, 7 years and 7 months, 5 years and 5 months and 5 years old (mean: 7 years and 9 months ± 38 months) when first seen in the FVMU. Mean weight was 5.5 ± 0.7 kg. The group of dogs existed of 9 females, of which 6 were sprayed, and 7 males whereof 3 were castrated. The following breeds were represented repeatedly; three Bullmastiffs,

two Bouvier des Flandres and two Labrador Retrievers. The other breeds were only seen once; English Springer Spaniel, Bernese Mountain Dog, Tibetan Terrier, Bordeaux Dog, Rhodesian Ridgeback, Cane Corso, Maltezer, Old English Sheepdog and a crossbreed of a Doberman. Mean age of dogs when first presented in the FVMU was 5 years and 5 months ± 44 months (range: 1 year and 1 month – 14 years and 6 months). Ranging from 7.3 to 59.1 kg, mean weight was 33.1 ± 13 kg.

Clinical presentation

The cats suffered respectively 2 days, 2 weeks, 9 months and 12 months (mean: 22 weeks ± 21 weeks) from symptoms of chylothorax before presented at the FVMU. For 14 dogs this period had a mean of 3 weeks ± 2 weeks (range: 1 day – 2 months). For the remaining two dogs the period of ongoing symptoms of disease before presentation at the clinic was unclear.

Table 1: Signalment and symptoms, dogs

#	sex	breed	weight	age	symptoms	duration
1	FN	Labrador Retriever	23.5 kg	7 y 8 m	dyspnea, decreased endurance, coughing (after effort), vomiting	1.5 weeks
2	FN	English Springer Spaniel	21.8 kg	2 y 1 m	dyspnea, abnormal breathing pattern, decreased endurance, abnormal respiratory sounds	1 month
3	FN	Bullmastiff	49.0 kg	5 y 3 m	dyspnea, abnormal breathing pattern, lethargy, vomiting	2 weeks
4	MN	Bernese Mountain Dog	59.1 kg	3 y 8 m	dyspnea, abnormal breathing pattern, decreased endurance, lethargy, coughing, anorexia, blue tongue, vomiting	1.5 months
5	FN	Tibetan Terrier	10.4 kg	9 y 10 m	dyspnea, abnormal breathing pattern, lethargy, coughing, eating less, collapse during effort	At least 2 months
6	F	Bordeaux Dog	39.5 kg	5 y 5 m	dyspnea, decreased endurance	unknown
7	F	Labrador Retriever	29.2 kg	1 y 5 m	dyspnea, abnormal breathing pattern, decreased endurance, coughing, collapse after effort, drinking more	3 weeks
8	F	Bouvier des Flandres	29.3 kg	4 y 3 m	dyspnea, decreased endurance, lethargy, blue tongue, eating less	1 month
9	MN	Rhodesian Ridgeback	36.7 kg	3 y 6 m	dyspnea, abnormal breathing pattern, coughing, anorexia, drinking more, sensitive throat	1 month
10	M	Bullmastiff	48 kg	1 y	dyspnea, lethargy, eating and drinking less, losing weight	2 weeks
11	FN	Cane Corso	30.9 kg	5 y 9 m	dyspnea, abnormal breathing pattern, decreased endurance, lethargy, eating and drinking less, fainting	1 week
12	MN	Maltezer	7.3 kg	11 y	dyspnea, anorexia, cyanosis, not drinking	1 day
13	M	Bouvier des Flandres	37 kg	6 y 7 m	dyspnea, abnormal breathing pattern, decreased endurance, lethargy, coughing, blue tongue, eating less, abnormal respiratory sounds, fainting,	2 weeks
14	FN	Bullmastiff	41.2 kg	1 y 11 m	dyspnea, decreased endurance, lethargy, anorexia, drinking less, abnormal respiratory sounds	2 weeks
15	M	Old English Sheepdog	33.5 kg	2 y 10 m	dyspnea, decreased endurance, lethargy, anorexia, blue tongue	unknown
16	M	Crossbreed Doberman	33.7 kg	14 y 6 m	dyspnea, abnormal breathing pattern, blue tongue, collapse after effort, losing weight	1 month

For each dog patient number (#), signalment and symptoms are given. The sex is described by F; female, M; male, N; neutered. Age is given in years (y) and months (m). The time of ongoing clinical symptoms before presentation at the clinic was given as duration.

Table 2: Signalment and symptoms, cats						
#	sex	breed	weight	age	symptoms	duration
17	MN	Domestic short hair	5.8 kg	13 y	dyspnea, coughing, anorexia, vomiting, blue tongue and collapse after effort	2 weeks
18	MN	Domestic short hair	6.5 kg	7 y 7 m	dyspnea, decreased endurance, coughing (mainly after effort), abnormal respiratory sounds, sensitive throat	9 months
19	MN	Domestic short hair	4.8 kg	5 y	dyspnea, abnormal breathing pattern, lethargy, anorexia	2 days
20	MN	Domestic short hair	5 kg	5 y 5 m	dyspnea, abnormal breathing pattern	1 year

For each cat patient number (#), signalment and symptoms are given. The sex is described by F; female, M; male, N; neutered. Age is given in years (y) and months (m). The time of ongoing clinical symptoms before presentation at the clinic was given as duration.

All animals were presented with dyspnea. Other symptoms mentioned by owners were abnormal breathing patterns (15 times), decreased endurance (11), lethargy (9), coughing (8), anorexia (7), cyanosis of the tongue (7), eating less (5), drinking less (4), collapse during effort (4), abnormal respiratory sounds (4), vomiting (3), sensitive throat (2), losing weight (2), drinking more (2) and fainting (2). Physical examination revealed tachypnea (16), abdominal breathing (9), pendulating respiration (9), hyperthermia (≥ 39,4) (5), weak pulse (4), considerable elevated hearth frequency (≥ 140 for dogs) (3).
Lung auscultation revealed increased lung sounds, especially dorsal (8), dorsal increased and ventral decreased lung sounds (7), decreased ventral lung sounds (2), both decreased and increased lung sounds on different spots of the thorax wall (1). In 6 patients auscultation of the heart was also weakened. Percussion of the thorax revealed a fluid line in 16 patients. In two patients dullness was noted during percussion, in one patient this was more obvious on the right side of the thorax.

Diagnostic tests
Triglyceride concentration of the thoracic fluid was measured in all patients, a mean of 15.85 ± 12.31 mmol per liter was found (range; 1.72 - 46.65 mmol per liter). When considering dogs only, the found mean was 13.29 ± 10.33 mmol/L and the cats had a mean of 26.11 ± 14.12 mmol/L. In 18 patients the triglyceride concentration of serum was also determined. Mean serum concentration was 0.56 ± 0.2 mmol/L. Looking at species apart, dogs had a mean TG concentration of 0.57 ± 0.21 mmol/L and the cats had 0.6 ± 0.18 mmol/L triglyceride in blood serum.
The amount of cholesterol in the thoracic fluid and blood serum was determined in respectively 14 and 12 of the dogs and 3 cats. The thoracic fluid had a mean cholesterol concentration of 2.24 ± 0.62 mmol/L. When taken only the concentrations measured in cats the mean was 2.6 ± 0.92 mmol/L, in dogs this was 2.16 ± 0.51 mmol/L. The cholesterol determination in blood serum showed a mean of 4.34 ± 0.99 mmol/L. The cats solely had a mean of 4.03 ± 1.4 mmol/L and the dogs on the other hand had a mean cholesterol concentration of 4.42 ± 0.85 mmol/L. Results per patient are given in table 3.

Surgery
Before undergoing surgery all patients had at least one, but often repeated, thoracocentesis. Thereby 15 patients were started at a low fat diet and 8 patients (of which 2 cats) had rutin administered. All patients were operated by, or under supervision of, three different veterinary surgeons. Mean duration of surgery was 133 ± 39 minutes. Dogs underwent surgery in mean time of 146 ± 34 minutes and cats in 91 ± 13 minutes. There was one complication during a secondary surgery, a patient had a cardiac arrest during induction and died. Abnormalities noticed during surgery were pleuritis (5), fibrinous material in the thorax (4), thickened and/or opaque pleurae (3), thickened pericardium (2), adhesions (2), epicarditis (1), possible pneumonia (1), abnormal pericardium (1), free mass in the pleural space (1), obvious enlarged lymphatic vessels (1), necrotizing mass at the dorsal side of the hearth around the caudal vena cava (1), extensive

emphysema alongside the whole aorta and into the abdominal cavity (1) and a focus of inflammation on the diaphragm (1) (Table 4).

Thoracotomy

15 patients, 13 dogs and 2 cats, were operated by thoracotomy. All but 3 dogs had, besides en bloc TDL, also SP performed. One Bullmastiff had TDL and SP done via two different thoracotomy sites during one surgery. The surgical time was unknown for 3 patients, the mean time for the procedure in the other 12 patients was 131 ± 35 minutes. When looked at the group of dogs separately the mean time of operation was 139 ± 32 minutes, whereas the surgery in cats took a mean time of 90 ± 19 minutes. In 3 patients there was also the need for lung lobe resection during the same surgery. One dog had a lung lobe torsion, lung lobe resection was performed but did not solve the chylothorax. Therefore 9 days after this operation TDL and SP was done.

A second surgery due to failure of first treatment for chylothorax was done in 3 dogs. One dog had SP with thoracotomy and CCA and omentalization via celiotomy performed, 12 days after first surgery. The second patient underwent CCA and omentalization by celiotomy 6 days after initial TDL and SP. The last patient died during anesthesia induction, the planned CCA and omentalization were therefore never completed.

Thoracoscopy

The remaining 5 patients, 2 cats and 3 dogs, underwent thoracoscopic surgery. They all had both en bloc TDL and SP performed, in a mean surgical time of 140 ± 45 minutes. When taken species separately the mean surgical time of dogs was 171 ± 31 minutes and for cats 93 ± 3 minutes. In this group one dog had secondary surgery. One month after the first operation, TDL with thoracoscopy was performed once again, this time with an approach from both the left and right thorax wall. In addition a laparoscopic CCA was carried out.

Recovery

Hospitalization was measured from day of first surgical treatment for chylothorax until day of discharge, see table 4. Mean hospitalization for all patients was 8 ± 4 days. When divided for the groups of thoracoscopic and thoracotomic treated patients the means were respectively 7 ± 4 days and 8 ± 4 days. Hospitalization for dogs had a mean duration of 8 ± 4 days, whereas for cats the mean stay took 6 ± 3 days.

Table 3: Triglyceride and Cholestrol concentrations of serum and effusion.

Patient	TGe	TGs	Ce	Cs
1	15.3	0.24	1.2	3.6
2	1.72	0.25	3.0	5.4
3	18.45	0.45	2.3	x
4	39.3	0.94	1.9	4.1
5	2.59	0.66	3.0	4.0
6	35.65	0.61	x	6.4
7	3.8	0.46	2.3	4.2
8	10.17	0.49	2.1	4.3
9	15.1	0.73	2.0	4.2
10	4.81	0.9	2.5	3.9
11	7.07	0.46	x	x
12	16.0	0.63	2.7	5.2
13	11.55	x	1.4	x
14	11.01	0.43	1.8	3.1
15	9.0	0.36	2.1	4.6
16	11.1	x	2.0	x
17	31.3	0.43	3.3	4.3
18	46.65	0.81	3.2	5.6
19	10.3	0.75	1.3	2.2
20	16.2	0.4	x	x

This table contains the results of analysis of thorax effusion and blood serum of all patients. All values are given in mmol/L TGe stands for concentration of triglyceride in thorax effusion and TGs for this concentration in blood serum. Cholesterol concentration in effusion (Ce) and blood (Cs) are also given.

Follow-up

The owners of the 2 dogs that died within 2 weeks after (secondary) surgery and of the dog that died during secondary surgery were notcalled for follow-up. From the remaining patients 1 cat and 2 dogs got lost to follow-up. 13 patient owners were interviewed by phone and one owner returned the questionnaire that

#	T/S	type	D	Notifications and 2nd surgery	H	result	status
1	S	TDL, SP	130 min.	pleuritis, fibrin	8	disease free	alive, 7.5 months p.s.
2	T	TDL, SP	120 min.		6	persistent chylothorax	euthanised 2 weeks p.s
3	S	TDL, SP	179 min.	abnormal pericardium	3	disease free	alive, 2 years and 2 months p.s.
4	T	TDL, SP	199 min.	lung lobectomy, free necrotizing mass	9	disease free	died due to histiocytic sarcoma 2 years p.s.
5	S	TDL, SP	204 min.	Pleuritis, enlarged lymph vessels **2nd surgery:** lapartotomic CCA, thoracoscopic TDL at both sides of the thorax (1 month later)	14 *(6)	persistent liquothorax (persistent chylothorax after 1st surgery)	alive, 3 years and 3 months p.s.
6	T	TDL, SP	108 min.		5	persistent liquothorax	euthanised 2 months p.s.
7	T	TDL, SP	115 min.		5	disease free	alive, 3 years and 8 months p.s.
8	T	TDL	121 min.	thickened and opaque pleura and mediastinum, thickened pericardium	5	disease free	alive, 3 years and 8 months p.s.
9	T	TDL, SP	167 min.	partial lung lobectomy, necrotizing mass around vena cava, pleuritis, fibrin	8	recurrent chylothorax after 2 years and 10 months	euthanised 3 years and 3 months p.s.
10	T	TDL, SP	?	thoracotomy at 2 places, , emphysema alongside aorta and in the abdomen	5	unknown	unknown
11	T	TDL, SP	101 min.	Fibrin **2nd surgery**: celiotomy for CCA and omentalization (6 days later)	11 **(5)	persistent liquothorax	euthanised 15 days p.s.
12	T	TDL, SP	?		7	disease free	died due to intestinal cancer 5 years and 2 months p.s.
13	T	TDL, SP	124 min.	extensive pleuritis, opaque pleura **2nd surgery:** celiotomy for CCA and omentalization	7	persistent chylothorax	died in second surgery, 2 months after first surgery
14	T	TDL, SP	180 min.	adhesion lung to diaphragm	6	recurrent chylothorax after 5.5 months	euthanised 5.5 months p.s.
15	T	TDL	154 min.	lung lobectomy **2nd surgery:** Celiotomy for CCA and omentalization, thoracotomy for SP (12 days later)	20 **(8)	disease free (persistent chylothorax after 1st surgery)	died due to malign lymfoma 5 years and 9 months after surgery
16	T	TDL	?	9 days earlier thoracotomy for lung lobectomy after lung lobe torsion. Pleura opaque and thickened, focal inflammation on diaphragm.	8	unknown	unknown
17	S	TDL, SP	90 min.	fibrin, thickened pericardium	5	persistent chylothorax	euthanised 8 days p.s.
18	S	TDL, SP	95 min.	pneumonia, epicarditis	4	disease free	alive, 11 months p.s.
19	T	TDL, SP	108 min.	lung lobectomy	4	disease free	alive, 4 years and 7 months p.s.
20	T	TDL, SP	71 min.	pleuritis with adhesions	10	unknown	unknown

Table 4: Type and course of surgery and final outcome

*This table reports for all patient numbers (#) whether they underwent thoracoscopy (S) or thoracotomy (T), the type of treatment that was done whereas TDL stands for thoracic duct ligation and SP for subtotal pericardectomy. The duration (D) was given in minutes. Hospitalization (H) was given in days. Hospitalization after secondary surgery was marked with *. The numbers marked with ** show duration of hospitalization after second surgery. Current status of the patient was given post-surgery (p.s.)*

was sent by mail. Mean follow-up time from surgery to time of death or research was 25 months, ranging from 9 days to 69 months.

Treatment Outcome

The outcome of treatment is displayed in table 4. After surgery 9 patients, of which 2 cats, became disease free and stayed disease free until follow-up or death with no relation to chylothorax (malign lymphoma, intestinal cancer and histiocytic sarcoma). Persistent chylothorax after surgery was seen in one cat and 3 dogs. One of those dogs died during induction of secondary surgery. The owners of two patients refused further treatment and chose for euthanasia, 8 days and 2 weeks after operation. The last dog that suffered from persistent chylothorax after initial surgery had repeated TDL and CCA performed in an additional treatment. After this surgery the aspect of chyle disappeared but the dog continued to produce pleural effusion in form of a liquothorax. Nevertheless this patient was still alive at time of follow-up. After discharge she receives palliative thoracocentesis two times per week, or more frequent in warm summer weather. Also a special diet composed by a nutritional expert, adapted to losses due to thorax drainage, and 750 mg rutin per day are administered. So far she had developed pneumothorax two times but besides that she does well according to the owner.

Persistent liquothorax did also occur after the initial surgery in two patients. They were both euthanized. One of them did have additional surgery 6 days after the first, but pleural effusion continued and euthanasia was performed 9 days later. The other one received rutin, low fat diet and palliative thoracocentesis for approximately 2 months, but despite this therapy the dog kept getting worse and was euthanized.

The 2 remaining patients had a recurrent chylothorax at 5.5 months and 2 years and 10 months after surgery. One was directly euthanized. The other patient had conservative therapy consisting of low fat diet, rutin administration and thoracocentesis for approximately 5 months until drainage was needed every six days and the owner decided to stop treatment and euthanasia was performed. At time of follow-up 9 of 17 patients were disease free or had been disease free until death, which is 53%. For the group treated with thoracoscopy this were 3 out of 5 patients (60%) and with thoracotomic surgery 50% of the patients, 6 out of 12, had a successful outcome. 2 out of 3 cats became disease free and for the dogs 50% of treatment turned out successful. The differences between those success percentages is not significant. Excluding the dogs that only had TDL, the success percentage of en bloc TDL in combination with SP is 47% (7 out of 15). Regarding only this combined surgeries, 40% of thoracotomy treatments had a successful outcome, whereas the thoracoscopic results remain 60%. This difference is also not significant. Figure 1 gives the survival curve of all patients, mean survival time after surgery was 194 weeks. When separated for both treatment groups (Figure 2), mean survival time after thoracotomy is 178 weeks and 136 weeks in the group of thoracoscopy patients. This difference between treatment groups was found to be not significant with the Log Rank test.

Discussion

As described above, the found results of treatment with thoracotomy and thoracoscopy were indeed similar, as was expected. The success of treatment with the combined en bloc TDL and SP on the other hand was, with 47% in the current study, lower than expected since for treatment with TDL and SP a mean success of 85% is reported, ranging from 57%-100%.(Allman et al. 2010; Bussadori et al. 2011; Carobbi, White, and Romanelli 2008; Fossum et al. 2004; Mayhew et al. 2012; McAnulty 2011)

Thereby, while working at this report, idiopathic chylothorax in dogs and cats seemed to be a relative unknown area in veterinary medicine, therefore there is chosen to share and discuss a broad set of data about the patients. Hence not everything described and discussed in this report will directly contribute to the research questions.

First of all, all four cats included in the current study were neutered males. Other studies, including studies with much larger patient groups, do not report a sex predisposition, therefore this finding seems to be a coincidence.(Fossum 2006; Fossum et al. 1991)

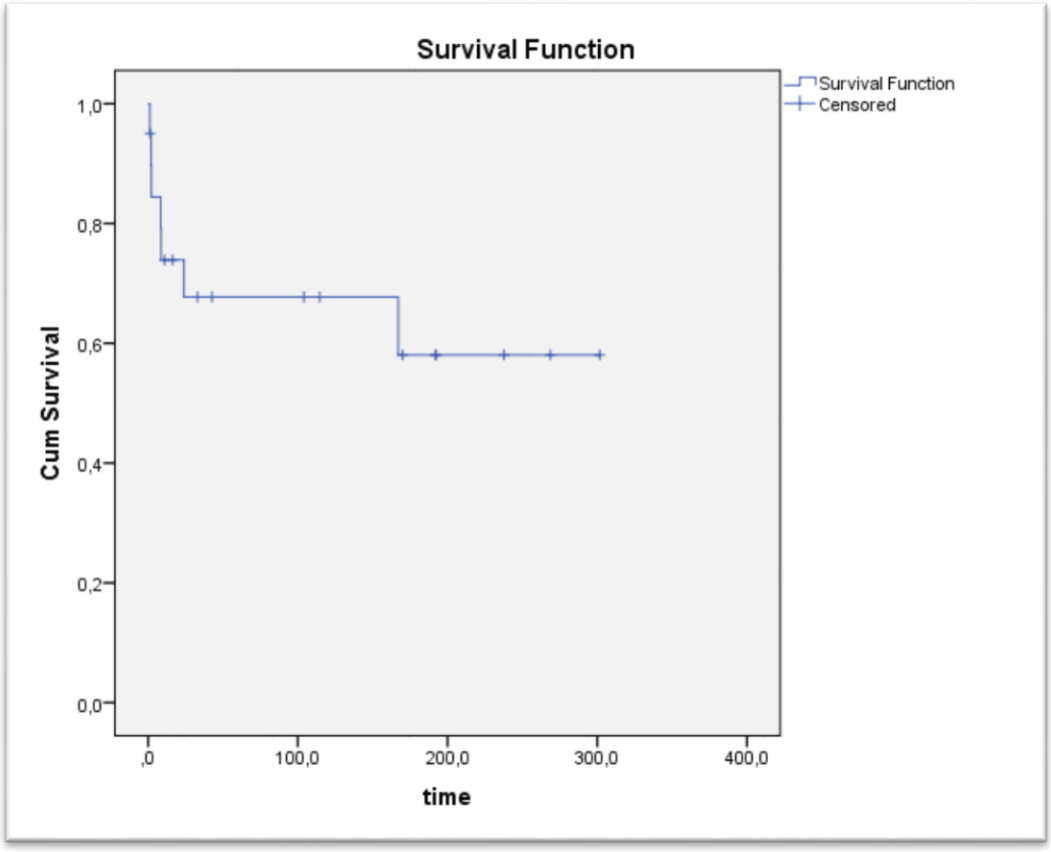

Figure 1: Cumulative survival analysis of all patients in a Kaplan Meier curve. Time is given in weeks.

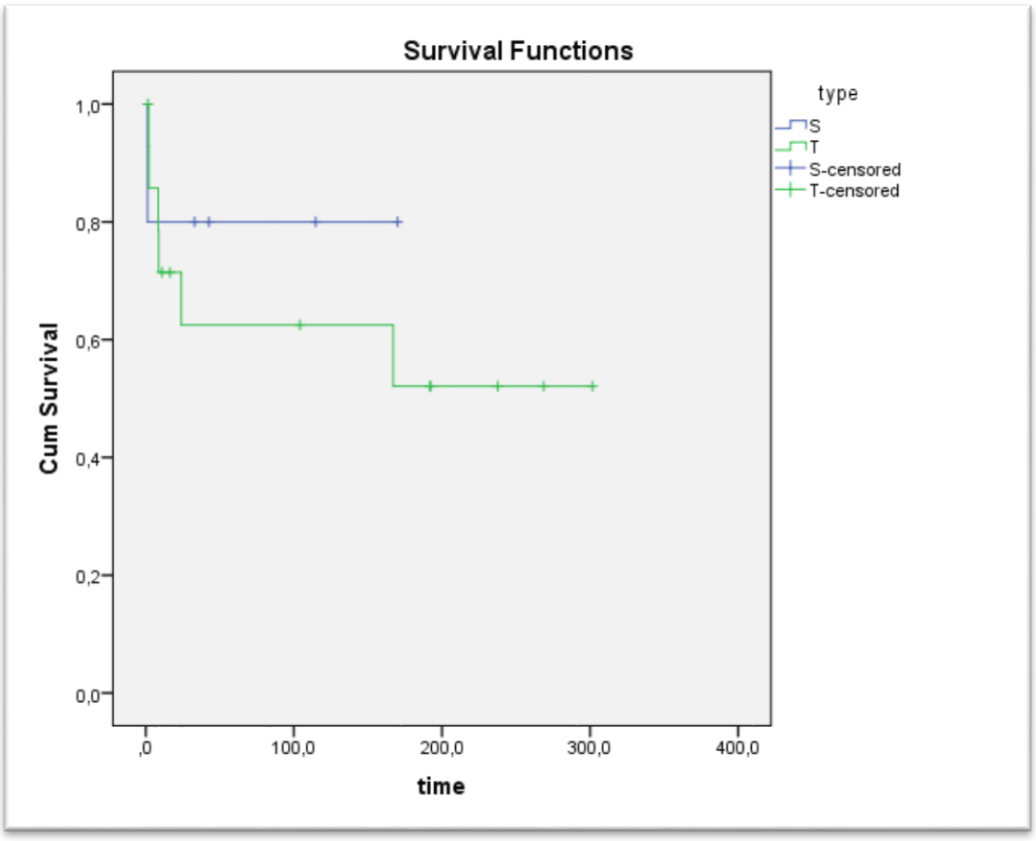

Figure 2: Cumulative survival analysis of patients treated with thoracoscopy (S) and thoracotomy (T). Time is given in weeks.

Furthermore the cats were, with a mean age of 93 months, older than the dogs at moment of presentation in the clinic. This finding, however, was also reported in earlier studies.(Fossum 2006; Stewart 2010; Sturgess 2001)

Also, the predisposition for development of chylothorax in several dog breeds is broadly discussed. In this study the following breeds were found repeatedly;
3 Bullmastiffs, 2 Labrador Retrievers and 2 Bouviers des Flandres. The first two breeds could be expected following a report of McAnulty in 2011, who reviewed 137 published cases whereof 7.4% were Labrador Retrievers and 5.8% Bullmastiffs. Bouviers des Flandres were not mentioned as broadly represented breed in chylothorax patients.(McAnulty 2011) Moreover, breed predisposition is difficult to determine in this rare disease, for example popularity of certain breeds in the researched area could influence results.

The mean weight of the dogs was 33.1 kg, which is in accordance with most other reports with means ranging between 27.1 kg - 32.5 kg. (Allman et al. 2010; Bussadori et al. 2011; Hayashi et al. 2005; Staiger, Stanley, and McAnulty 2011) Suggesting that, despite the often broad range, dogs that weigh around 30 kg are affected mostly.

Furthermore, the most important symptoms for chylothorax found in patients of the current study seemed to be dyspnea, abnormal breathing patterns, decreased endurance, lethargy, coughing, anorexia and cyanosis of the tongue. These were all expected since they are all symptoms that belong to respiratory problems or overall sickness and have been reported before in chylothorax patients. (Singh 2012b; Sturgess 2001) The dogs had a reported duration of symptoms of maximal 2 months (mean: 3 ± 2 weeks) when presented in the FVMU. The cats on the other hand were presented much later, with a mean of 22 ± 21 weeks, due to the two cats that suffered from symptoms for 9 and 12 months. The latter was treated medically initially. With administration of rutin and a low fat diet the cat did well for over half a year but eventually symptoms returned and medical treatment was not satisfactory anymore. This difference of symptom duration regarding to the dogs could be a coincidental finding due to the small group of cats. It could also be that the onset of disease in cats is milder which makes owners wait longer with visiting a veterinarian. Fossum reports that cats with chylothorax often have symptoms, especially coughing, months before presentation at a veterinary clinic.(Fossum 2006) Moreover the reported duration of symptoms by owners is not always reliable. As reported by Fossum et al. patients with, according to the owners, a recent onset of disease turned out to have severe fibrosing pleuritis.(Fossum et al. 2004) This was also seen in the current study, for example a patient with extensive fibrosing pleuritis where the owners noted symptoms for only 1.5 week. However, the duration of symptoms seems to be no good predictor for severity of fibrosing pleuritis or successful outcome of treatment in patients with chylothorax. Fossum et al. even hypothesized that clinical signs begin to show after the pleura are significantly thickened and thereby have a reduced fluid absorption capacity or absorption has totally stopped. (Fossum et al. 2004) So although there seems to be a remarkable difference of symptom duration between the species, it is not known whether this applies in general and the effects on severity of pleuritis and on treatment outcome seem to be little.

Besides the cat that greatly improved clinically for several months after rutin administration, some improvement was also reported by the owners of one other dog that received rutin in its initial treatment. The owners of the other 6 patients that received rutin before surgical treatment reported no obvious beneficial effect. Rutin, which is a nutritional supplement, can be purchased over-the-counter and is reported to relieve clinical symptoms and sometimes even results in resolution of chylothorax, especially in cats.(Gould 2004; Kopko 2005; Thompson, Cohn, and Jordan 1999) Although the working mechanism remains unknown and it is possible that reported resolution of disease was in fact spontaneous resolution, there have been no negative side-effects reported. Therefore rutin could be used as medical treatment for patients with chylothorax or as an additional measure after surgery. (Singh 2012a)

In diagnosing chylothorax the hardest part is confirming whether the fluid is indeed

chyle. In this study the fluid was called chyle when the concentration of triglycerides (TG) in the thoracic fluid was higher than the concentration triglycerides in the blood serum. In two dogs of the current study triglycerides in blood serum were not measured, but their effusions had TG concentrations of 11.1 and 11.55 mmol/L, both well beyond the upper reference value of blood serum TG of 1.45 mmol/L.[b] Therefore this patients almost certainly had chylous effusion and were still included in the study.

Another criterion to determine whether the fluid contains chyle, used in other institutes is the cholesterol : triglyceride ratio, which has to be less than 1 in chylous effusion.(Carobbi, White, and Romanelli 2008; Fossum, Jacobs, and Birchard 1986; Sturgess 2001) In the current study two patients, numbers 2 and 5, did not meet this condition. Surgical treatment in both of these patients resulted in a persisting chylothorax with effusion TG concentrations even higher than measured before operation. One patient was euthanized, the other patient received a second surgery which resulted in a persistent liquothorax. Therefore, unless only 2 patients had a C:TG ratio above 1 prior to surgery, based on treatment outcome this could be a negative indicator for surgical treatment. But further study with a larger patient group is needed to search for this possible predictive factor.

On the other hand, the use of the C:TG ratio of less than 1 as crucial criterion for diagnosis of chylothorax is questioned. Waddle and Giger report that 12% of dogs and 50% of cats with nonchylous effusion turned out to have a C:TG below 1 as well.(Waddle and Giger 1990) Whether there are chylothorax patients falsely excluded with this parameter was not reported. The same study reports that a better predictive value to determine chylous effusion is the use of TG concentration of pleural fluid. Which was above 1.13 mmol/L for all animals with chylous effusion and beneath this concentration for all patients with nonchylous effusion in that study.(Waddle and Giger 1990) Since the lowest measured pleural TG concentration in patients of the current study was 1.72 mmol/L, all patients met this criterion. This further suggests that the criterion of a C:TG ratio less than 1 could, besides including animals with nonchylous effusion, also exclude true chylothorax patients since two patients of this study had a ratio above 1 but a TG concentration of effusion above 1.13 mmol/L. An earlier published report also found significant differences between chylous and nonchylous effusions in dogs and cats, triglyceride concentration of pleural fluid is higher and C:TG ratio is lower in patients with chylous pleural fluid. (Fossum, Jacobs, and Birchard 1986) One should therefore not conclude based on C:TG ratio only, but also consider TG concentrations of pleural fluid.

The reference range of serum triglyceride for dogs is 0.33-1.46 mmol/L[b], for cats this range was not found. When analyzing the serum TG concentrations measured in patients of the current study, remarkably all but one patient (0.94 mmol/L) had concentrations below or at the median of the reference rage; 0.9 mmol/L. In the study of Staiger et al. reported serum concentrations were also below or at 0.9 mmol/L .(Staiger, Stanley, and McAnulty 2011) Furthermore mean serum TG concentrations reported in other studies were 0.67 mmol/L in 12 dogs (Viehoff and Stokhof 2003) and 0.79 mmol/L in 11 dogs (da Silva and Monnet 2011), both also under the median of the reference range (0.9 mmol/L). The lower blood serum TG in chylothorax patients does not seem illogical, considering that chylothorax patients lose a lot of chyle in the pleural space, which therefore does not reach the circulation.

Moreover when looking at biochemistry outcomes, it was obvious that the mean concentration of TG in the pleural fluid of cats was almost twice as high as in dogs. Possible causes could be that the cats consumed more fat with their diet and thereby producing chyle with a higher TG concentration. This is unknown since the diets of the dogs and cats at time of presentation at the clinic were not reported. Another possibility could be that the pleura of cats have lower TG absorption capacity than the pleural tissue of dogs. Which should be very specific for triglycerides then, because the cholesterol concentrations in effusion were similar to the concentrations found in the dogs. Whether cats with chylothorax have higher pleural triglyceride concentrations than dogs in general, and the possible underlying cause, is

not reported before and should be further researched with bigger patient groups.

Further, after confirming the chylous content of the effusion, and thus chylothorax, possible causes for the chyle leakage needed to be ruled out before calling the chylothorax idiopathic. The idiopathic aspect of diagnosis was not completely sure in some patients of this study. One patient, number 16, had a lung lobe torsion, which is known as a possible cause of chylothorax. Although lung lobe torsion usually causes serosanguineous effusion unless it compresses and thereby obstructs the vena cava which then causes chylous effusion. On the other hand patients with any form of thoracic fluid have a higher risk of lung lobe torsion, therefore the torsion could also be caused by the pre-existing chylothorax. (da Silva and Monnet 2011; Singh 2012b; Sturgess 2001) So when the lung lobectomy had not eliminated the chylous effusion after 9 days, TDL was performed. Because of the persistent chylothorax after lung lobectomy it was concluded that the lung lobe torsion was not the only reason for chylothorax, therefore this patient was included in this study. In another patient a necrotizing mass around the caudal vena cava, just dorsal of the heart, was found during surgery. This could be the cause of the leakage of chyle since it could block the vena cava or otherwise caused to hinder the chyle excretion into the venous system.(Singh 2012a) Planned TDL and SP were still carried out after this discovery and the outcome was successful until recurrence of chylothorax almost 3 years later. A possible cause for the recurrence was not examined. Furthermore patient 6 had malignant lymphoma in the mediastinum at the end of 2009. When presented with chylothorax in June 2010 there were no signs of a remaining tumor. The question is though whether the chylothorax can be caused by damage related to the tumor or its treatment, which should make it non-idiopathic. The last case with a difficulty in the diagnostic process was patient 12, this dog was hit by a bus 4 weeks before presentation with chylothorax. Most human patients with chylothorax have trauma as underlying cause, in animals this is seen less.(Lyon et al. 2013) In the accident the thoracic duct could be damaged and therefore this trauma could result in chylothorax. But the onset of symptoms seemed very acute and started only one day before presentation at the clinic. When related to the trauma one should expect an acute onset closer to time of trauma or a progressive development when a small leak is formed at time of trauma, but the possibility of a traumatic etiology cannot be excluded based on the case report. However, due to the small research group, it was decided to include all patients described above despite some remaining questions about the idiopathic diagnosis.

The mean surgery time for all thoracoscopic surgeries was, with 140 minutes, slightly longer than the overall mean duration of 131 minutes in thoracotomy. Duration of both procedures was shorter in cats than in dogs. Furthermore in cats there was little difference in surgery time between thoracoscopy (90 and 95 minutes) and thoracotomy (71 and 108 minutes) and the overall mean time of surgery was 91 minutes. For dogs on the other hand the difference between both procedures was obvious. Thoracotomy in 10 dogs had a mean duration of 139 minutes, the 3 thoracoscopic surgeries took approximately half an hour longer (mean 171 minutes). Although this latter group of dogs is small, a mean surgery duration of 177 minutes in 6 dogs and 184 minutes for 12 dogs that received thoracoscopic TDL and SP were reported in other studies. (Allman et al. 2010; Mayhew et al. 2012) Therefore this seems a reasonable expectation for surgery time. So in dogs thoracoscopic surgery takes rather more time than thoracotomy, in cats this difference seems not that obvious.

During thoracoscopic surgery the patients needed to be rotated form ventral to dorsal recumbency to accomplish the subtotal pericardectomy. This probably is a large factor causing the surgery to take longer than when thoracotomy is performed. (da Silva and Monnet 2011; Staiger, Stanley, and McAnulty 2011) The prolongation of surgical treatment due to additional SP is further supported by a reported mean duration of 59 minutes for solely TDL by thoracoscopy performed in 5 healthy dogs. (Radlinsky et al. 2002) Moreover, thoracoscopic surgery could be more time consuming than thoracotomy procedures in

general. No report of a large scale comparison between surgery duration of thoracotomy versus thoracoscopy was found. Furthermore comparison of thoracic surgeries is difficult because the course is depending on multiple factors as width and depth of the thorax and possible extent of retraction of the chest wall.

One patient died during induction of anesthesia for a second surgery. This dog did not have thoracocentesis before induction because he did not tolerate this. After the heart stopped reanimation and thoracocentesis were performed, though complicated due the present chylothorax, but this was unsuccessful. The reason for the cardiac arrest is unknown, but might have something to do with not having thoracocentesis before surgery, since a chylothorax has a negative influence on respiratory and circulatory function of the patient.(Fossum 2006; Singh 2012a) Therefore, when possible, thoracocentesis before surgery might be preferred. This was the only complication reported during surgery. Records of thoracoscopic surgery in this study did not state any difficulties related to the technique. The feasibility of the non-invasive surgery techniques for TDL and SP was previously confirmed in other studies. (Allman et al. 2010; Bussadori et al. 2011; Mayhew et al. 2012; Radlinsky et al. 2002; Radlinsky 2009)

Furthermore, besides the planned surgical procedures as described in materials and methods, one cat and 3 dogs also needed lung lobectomy due to severe lung damage or, in one case as reported above, due to lung lobe torsion. In a research paper published by Da Silva and Monnet in 2011, lung lobectomy was found to be no negative indicator for prognosis. In that study 4 of the 11 patients needed lung lobectomy. At time of follow-up they had a similar percentage of disease free animals as the 7 patients that did not have lung tissue removed.(da Silva and Monnet 2011) Looking at the results of the lung lobectomy patients of the current study one finds that the cat is still alive and disease free at time of follow-up, 4 years and 7 months later. One dog was lost in follow-up and the other two lived respectively 2 years and 5 years and 9 months after surgery, after which they died of causes unrelated to their prior chylothorax. Therefore, as far as known, in 3 out of 3 animals disease resolved, which is even a higher success percentage than found in the total study. So the data found in the current study are consistent with the conclusion of Da Silva and Monnet.

In the 5 patients treated with thoracoscopy, TDL was done in different ways. In 4 patients the tissue that is normally ligated during en bloc TDL with thoracotomy, was now coagulated with LigaSure[a]. Coagulation was done one or several times, in 2 cases the mediastinal tissue was also divided afterwards. Moreover, in one thoracoscopy patient the tissue was clipped with endoclips and, during secondary surgery performed in this patient, multiple ligaclips were placed approached from both sides of the thorax. So although en bloc TDL was performed in all patients, the used technique differed, which could influence the comparison and the final result. Due to the small group it is hard to tell which technique is better. In the patient (number 5) that had ligation performed with clips the first treatment resulted in a persisting chylothorax. After receiving a secondary surgery a liquothorax persisted. Therefore one could think that treatment by clipping is less effective than tissue coagulation. The failure of treatment in patient 5 is, although, more likely due to other, yet unknown, factors since efficiency of clipping of the thoracic duct was reported earlier. In a study of Radlinsky et al. TDL with thoracoscopy was done in 5 healthy dogs by placing clips, lymphangiography after ligation showed total closure of the TD and its branches.(Radlinsky et al. 2002) Thereby thoracoscopic clip application for TDL was also used in clinical treatment of chylothorax patients in combination with SP, resulting in success rates of 86% (Allman et al. 2010) and 100% (Mayhew et al. 2012). Therefore successful ligation with clips has been proven. Successful closure of lymph vessels by sealing, on the other hand, is also published. For example quick and strong tissue coagulation by LigaSure was reported in porcine models. An advantage of tissue coagulation over clipping is that the LigaSure changes the structure of the tissue permanently at site of ligation, whereas clips can dislodge. (Novitsky et al. 2005) This sealing of tissue was also used clinically, two cats had thoracoscopic en bloc sealing of the thoracic duct performed with LigaSure and had

additional subtotal pericardectomy. Chylothorax resolved in both cases. (Haimel, Liehmann, and Dupré 2012) So, differences between the ligation methods could be further researched in prospective studies with standard protocols for both techniques and larger patient groups, but so far both ligation techniques seem feasible. (Haimel, Liehmann, and Dupré 2012; Novitsky et al. 2005)

Results for different surgical treatment procedures for idiopathic chylothorax have been published and set the expectations for the current study. For example, TDL as single treatment has a reported success rate of 50-60% in dogs, for cats this number is even lower and lies around 40% or less. (Fossum et al. 2004; Fossum 2001; Hayashi et al. 2005) When ligation of only the thoracic duct and its found collaterals is done, there is a risk of missing a branch which can result in persistent chylothorax. In one study of 22 patients, 4 of 6 dogs with persistent chylothorax were re-operated and turned out to have one large collateral lymph vessel that bypassed the earlier placed ligatures. (McAnulty 2011) Thereby a cadaver study in healthy animals found bilateral or even multiple branches of the TD with lymphangiography. Thereby most of the bilateral branches had transverse communications. (Radlinsky et al. 2002) So broad dissection of the whole mediastinum seems important when ligation of single branches is carried out, otherwise there is a great chance of missing a branch of the TD. The exact impact of missing a vessel is unknown, however, seemed the cause of persistent chylothorax in the study of McAnulty et al. Considering the low success percentage of TDL, missing a branch could be a big problem in this treatment technique. Especially when the missed vessel had transverse connections with the ligated TD caudally from the ligation site, because the chyle could continue its flow through the TD and still leak through the lymphangiectasis. But identification of single branches of the thoracic duct can be difficult in chylothorax patients since the mediastinal tissue can be thickened and opaque. Primarily when looking for tiny branches in cats and small dogs. Therefore the en bloc technique might be more desirable. (MacDonald, Noble, and Burrow 2008)

In the current study en bloc TDL was used. This technique is only described occasionally in other studies and was mostly done when identification of single branches failed. In a cadaver study of healthy dogs the en bloc ligation of the thoracic duct did successfully block all chyle flow in 13 of 14 dogs, thus in 93%.(MacDonald, Noble, and Burrow 2008) However this success rate can probably not be extrapolated to treatment of living chylothorax patients because both the anatomy and state of the mediastinum and the thoracic duct and its branches could be different from that of healthy dogs. (MacDonald, Noble, and Burrow 2008) Thereby the reaction of living tissue on the blockage of the thoracic duct is not taken in consideration in a cadaver study. Despite this complicating factors in patients, en bloc TDL still seems a successful technique to fully ligate the thoracic duct. Unless the bigger chance on ligating all branches of the TD at once with the en bloc technique, the clinical result of treatment does not seem to be more successful than normal TDL. In one study chylothorax patients were only treated with en bloc TDL which resulted in 50% success.(Viehoff and Stokhof 2003) The reason for failing of this treatment in half of the chylothorax patients is unknown. Failure could simply be caused by missing one collateral of the thoracic duct unless the used en bloc ligation, which could have been demonstrated by performing post-operative imaging of the TD. Numerous other theories have also been mentioned, for instance the formation of new collaterals or opening of inactive, patent branches that have the same course as the original thoracic duct.(Hayashi et al. 2005; MacDonald, Noble, and Burrow 2008) The latter was actually seen in a study of Kerpsack et al, where lymphangiography after surgery showed total thoracic duct ligation but chylothorax persisted and 50 days later a new lymphangiogram demonstrated new TD branches with lymphangiectasis.(Kerpsack, Smeak, and Birchard 1995; Viehoff and Stokhof 2003)

Besides a (theoretically) bigger chance of ligating al TD branches, another advantage of en bloc TDL is that there is less need for laparotomy to stain the lymphatics which results in less invasive and shorter

surgery.(MacDonald, Noble, and Burrow 2008; McAnulty 2011; Viehoff and Stokhof 2003)

There have been described multiple techniques to visualize the lymphatic vessels. Traditionally feeding fatty oil or cream was used but these results were found to be unsatisfactory in most dogs. (Radlinsky et al. 2002) However the value of lymphangiography or coloration of the lymphatics before TDL or CCA is widely discussed. Some articles advocate visualization of lymph vessels,(Fossum et al. 2004; Mayhew et al. 2012; Sicard, Waller, and McAnulty 2005) others state that the use of staining before TDL does not change the success rate.(Staiger, Stanley, and McAnulty 2011)

Furthermore lymphangiography after TDL to check complete closure is also advocated by some articles. Although this confirmation of closure does not provide certainty for the long term outcome of treatment.(Hayashi et al. 2005; Singh 2012b; Viehoff and Stokhof 2003) For example Hayashi et al. report recurrence of chylous effusion in 5 out of 18 cats after complete closure was checked. Another study reports up to 40% persisting effusion after control of full ligation.(Hayashi et al. 2005; Singh 2012a) This could be due to opening of non-patent branches of the TD or formation of collaterals around the ligation site.(Singh 2012a) One author states that in 13 years of treating chylothorax, performing lymphangiography after TDL changed course of treatment in only one case.(McAnulty 2011)

Thereby there has been reported that dissection around the TD without actual ligation could be enough to temporarily stop the flow through the thoracic duct. Therefore one could falsely conclude closure of the TD after surgery when performing lymphangiography.(Martin et al. 1988) Although this phenomenon seems to be never studied further and techniques used in lymphangiography will be improved since the writing of Martin et al. this finding could further doubt the value of lymphangiography post-surgery. Furthermore the quality of post TDL lymphangiography is reported to not always be sufficient to conclude total ligation of the TD and its branches. (Allman et al. 2010; Fossum et al. 2004; Mayhew et al. 2012) There was no use of lymphangiography in the current study.

Injection of methylene blue (MB) is another frequently used technique, which helps the surgeon identifying the thoracic duct and its branches, or other lymphatic structures, during surgery. Common concerns for the use of methylene blue are the hemolytic character or chance on renal failure due to high dose of MB.(Fossum 2001; Singh 2012b) In studies about chylothorax treatment where MB was used for staining lymphatics, the used MB was diluted and none of them report complications. (Allman et al. 2010; Mayhew et al. 2012; McAnulty 2011) Furthermore multiple studies report that MB injection in mesenteric or popliteal lymph nodes enables good vision of thoracic and abdominal lymph vessels and was helpful in identifying small TD branches. (Mayhew et al. 2012; McAnulty 2011; Radlinsky et al. 2002; Sicard, Waller, and McAnulty 2005)

In the current study 3 dogs had diluted methylene blue (MB) injected during secondary surgery, to color the cisterna chyli before ablation. MB was injected respectively in a mesenteric lymph node, a lymph node associated with the colon and in the popliteal lymph node. Although there were no signs of intoxication noted, the attempts were unsuccessful because there was no significant coloration of the cisterna chyli. Failure of good coloration with MB was also reported by Allman et al., when after TDL methylene blue was injected in the mesenteric lymph node or cutaneous in the popliteal lymph node. (Allman et al. 2010)

So apparently the value of methods for visualization seem to be controversial. Thereby reports of TDL with and without the use of identification of the lymphatics show similar success rates. Performing this techniques can prolong surgery and thereby anesthesia time and increase treatment costs. Furthermore in cats staining methods can be extra difficult due to their smaller lymph vessels and the higher amount of fat in the mesentery. (Fossum 2001; Singh 2012b) One should therefore carefully consider all advantages and risks when determining whether to implement a visualization technique in treatment protocol or not.

Since TDL seems to fail in half of the patients, there have been described additional treatments. The combination of en bloc TDL and SP, as done in most patients of this study, is published only once before by Bussadori et

al. They performed en bloc TDL, subphrenic pericardectomy and thoracic omentalization on 9 dogs and 4 cats. Eventually in 3 of 4 cats (75%) and 8 of 9 dogs (89%) chylothorax resolved. (Bussadori et al. 2011) Similar success rates are reported earlier for regular TDL and subtotal or subphrenic pericardectomy, namely between 57% - 100%, with a mean success of approximately 85%. (Allman et al. 2010; Bussadori et al. 2011; Carobbi, White, and Romanelli 2008; Fossum et al. 2004; Mayhew et al. 2012; McAnulty 2011) The combination of TDL and SP might even be considerd as the current standard treatment for idiopathic chylothorax. (Singh 2012a)

When evaluating outcome of surgical treatment in the current study, it was only considered to be successful when the patient becomes free of disease. Contrarily, when a patient continued to have signs of chylothorax or liquothorax, or eventually redeveloped symptoms in time, the outcome was considered as failure. The difference between persistent or recurrent disease in the current study was determined arbitrarily, because no regular medical imaging was performed after discharge. For example dog 13 had 2.5 liter of chylous like fluid removed one month after surgery. This was considered to be a persistent chylothorax because the macroscopy of chyle is very specific and during hospitalization the thorax drain produced effusion that sometimes had a chylous aspect. Nevertheless this patient could theoretically also have a high productive recurrent chylothorax, because the drain was minimally productive when removed. So for more precise determination of treatment outcome patients should be examined on regular basis after discharge.

The definition used for disease free is no signs of clinical symptoms of chylothorax. Therefore five patients that had mild pleural effusion on follow-up radiography but had no clinical signs were still considered disease free. When clinical signs started again in two patients after respectively 5.5 months and almost 3 years, this was both called recurrence, and not persistent, chylothorax. Another study found evidence of existing mild pleural effusions in all 10 of 11 dogs that had radiography in follow-up after surgical treatment of chylothorax. They reported recurrence of chylothorax in only 2 patient. (da Silva and Monnet 2011) So some form of pleural effusion after treatment does not automatically mean failure of treatment. Furthermore this remaining pleural effusion can eventually resolve, as seen in other studies. For example Carobbi et al. describe mild pleural effusion in two dogs seen on radiography both one month and three months after surgery, which had resolved 4 months later.(Carobbi, White, and Romanelli 2008) This temporarily remaining effusion is thought to be caused by chronic pleuritis, which can resolve after removing the possible cause; the leakage of irritating chyle.(Viehoff and Stokhof 2003) So some form of pleural effusion in dogs that have clinical resolved chylothorax after surgery is commonly seen. One could question if this outcome is truly a form of success, because chronic contact with effusion can cause the pleura to become progressively inflamed, which can give the patient serious health issues. (Mayhew et al. 2012)

Furthermore, in one dog of the current study effusion production short after surgery had a higher volume of fluid and content of triglycerides than before treatment but still became disease free afterwards. Therefore one should not conclude to soon about final result of surgery. This is also stated by Singh et al., they saw differences in time of resolving of chylothorax ranging from 1 to 50 days after successful TDL and SP. (Singh 2012a)

Considering the described terminology for treatment failure and success above, follow-up results were evaluated. Long term follow-up for determination of final treatment outcome was, amongst others, advocated by Da Silva and Monnet. They state that recurrence of disease can occur past 20 months after surgery.(da Silva and Monnet 2011) This observed late return of disease was also seen in this study, where dog 9 had recurrence of chylothorax after almost 3 years. Mean follow-up time in this study was 25 months. In the group of dogs that were still alive and disease free at time of follow-up, the shortest follow-up period was 8 months.

Final long term success of treatment in the current study was 53%. When specifically evaluating treatment outcome of en bloc TDL and SP and thus exclude patients that received

TDL only, treatment turned out to be successful in 7 out of 15 patients (47%).

So unless the fact that the used treatment methods have all been reported to be successful before (both en bloc TDL and SP, performed either by thoracotomy or thoracoscopy) the final outcome of treatment in this study is lower than expected, considering earlier studies report success rates of 57%-100% with a mean of approximately 85%.(Allman et al. 2010; Bussadori et al. 2011; Carobbi, White, and Romanelli 2008; Fossum et al. 2004; Mayhew et al. 2012; McAnulty 2011)

First of all, a report of Fossum et al. suggests that the experience of the surgeon has an influence on the success rate. They state that, in the second half of their research group, all patients had a successful outcome. So they hypothesize that in this last group there was more experience with the procedure and this positively influenced the results. (Fossum et al. 2004) In the current study all surgeries were performed or supervised by three different surgeons. The largest part of thoracotomic surgeries (13 of 15 procedures) were done by one single surgeon. The observed increase of success in time, as described by Fossum et al., was not noticed in the current study. Despite that this influence did not seem to be clear in our study, it seems logical that experience with the procedure can have a positive influence on surgery. Treatment should therefore be performed or supervised by an experienced surgeon when possible.

One possible reason for this lower success rates might be that there were patients with underlying causes of chylothorax that were not discovered during the clinical workup. In a study of Allman et al. published in 2010 both idiopathic and non-idiopathic chylothorax patients were treated with thoracoscopic TDL and SP. In that study 6 out of 7 dogs with idiopathic chylothorax became clinically disease free, the seventh dog was euthanized due to systemic inflammatory response syndrome 1 day after surgery. The non-idiopathic patients (diagnosed with chylothorax due to pericardial disease, fungal disease, right ventricular enlargement and trauma after surgery) on the other hand did not have this high success rate since in only 2 of 5 patients chylothorax resolved. The other 3 dogs had a persistent liquothorax or recurrent chylothorax. Which suggests that the treatment with TDL and SP has a better prognosis in idiopathic cases of chylothorax. (Allman et al. 2010) Despite that the performed treatment of TDL in combination with SP in the study of Allman et al. was quite similar to the treatment described in the current study, the outcome is not similar since fewer patients became disease free. Allman et al. report 86% success in the group of idiopathic chylothorax patients, whereas only 47% of patients resolved of chylothorax in the current study. Therefore it could be that the present study had patients with non-idiopathic chylothorax amongst the patient group. Among the 4 patients described earlier in this discussion, where the diagnosis of idiopathic chylothorax was considered questionable due to lung lobe torsion, a necrotizing mass around the vena cava, previous mediastinal tumor and possible trauma due to an accident, treatment success was low. One got lost to follow-up, from the other 3, only one had long term successful outcome of treatment. So thorough medical imaging and further testing for underlying causes should be performed in the diagnostic process.

In accordance with this theory, the difference in found success rates could be also caused by an unequal amount of patients with undiagnosed underlying restrictive pericardial problems in the small patient groups of published reports. Which is difficult to diagnose and the impact of this condition on the incidence of chylothorax is unknown. (McAnulty 2011) In those patients the direct cause of chylothorax would be taken away by performing SP, and therefore resolving of the chylothorax would be caused.(McAnulty 2011) Thereby the etiology of idiopathic chylothorax is unknown and other causes of chylothorax are associated with evaluated right-sided pressure of the venous system. (Fossum et al. 2004) Therefore it could be that high right-sided pressure has also a role in some patients with, the so far considered, idiopathic form of chylothorax. Nevertheless not all animals with diseases that elevate venous pressure develop chylothorax. This might be explained by the evidence of the ability to form new lymph drainage routes when necessary, for example

after TDL. The chyle drainage system seems to be adaptive to different conditions. (MacDonald, Noble, and Burrow 2008; Sicard, Waller, and McAnulty 2005; Singh 2012b) Why some animals with evaluated right-sided pressure do develop chylothorax, while others do not, remains unknown and should be subject of further research and could contribute to further understanding of idiopathic chylothorax.

Keeping the possible role of high venous pressure in mind one finds multiple studies reporting a thickened pericardium, most likely caused by inflammation due to contact with the irritating chyle. The thickened pericardium could cause elevation of venous pressure in the large veins around the hearth and thereby reinforce the chylothorax by hindering the TD to empty in the venous circulation. The aim of performing SP additionally to TDL is to reduce this right-sided pressure of the venous system. (Fossum et al. 2004; McAnulty 2011) Thickened pericardium was also seen in patients of the current study, for 6 dogs the removed pericardium was researched pathologically. All six were diagnosed with moderate to severe pericarditis.

Moreover, in a study of McAnulty published in 2011 the central venous pressure (CVP) was measured immediately before and after SP in 8 dogs, whereof only one dog had a reduced mean CVP. Strictly seen CVP is a doubted measure for right-sided pressure because it is influenced by multiple other factors such as disease conditions, anesthesia and overall status of for example hydration and blood pressure. Furthermore it might be that a rapid change of CVP is not to be expected because contractility of the heart needs time to recover.(McAnulty 2011) Therefore the hypothetical working mechanism behind SP, the decrease of venous pressure, cannot be declined based on this results.

The effect of pericardectomy on the venous pressure could be in correlation with the amount of pericardium that is removed. In the current study subtotal pericardectomy is performed, whereas in some other studies subphrenic pericardectomy was done. With the latter technique more pericardium is removed. Comparing the exact amount of eliminated pericardium and its effect is difficult. This was done by McAnulty, he states that the amount of removed pericardium does not seem to be, solely, responsible for the different results.(McAnulty 2011) So therefore the differences in removed pericardial tissue between studies is most likely not the cause for the large difference of success.

Another reason for not reaching the same success with combining TDL and SP as published in other reports, might be that in our study en bloc TDL was used. In one study of Sicard et al. TDL was performed in three healthy beagles. After approximately one month the newly formed lymph drainage system was evaluated. In all three dogs the chyle flow was taken over by the azygous vein. (Sicard, Waller, and McAnulty 2005) This might probably be what happens in most cases after TDL and TDL+SP procedures. Yet in the current study en bloc TDL was performed, thereby the azygous vein was also ligated and will therefore probably not be the new drainage route for the chyle. The newly formed drainage route after en bloc TDL was not inspected in the current study and is not reported before. So when en bloc TDL is performed instead of ligation of thoracic lymph vessels only, it could be that an alternative new drainage develops and additional SP is less useful. Although in the study of Bussadori et al. where en bloc TDL was performed, similar success rates were reached as expected with regular TDL and SP. Therefore a successful combination of those techniques does seem to be possible. So to find out what possibly goes wrong after surgical treatment with en bloc TDL combined with SP, the differences in newly formed lymph drainage and place of emptying in the venous system after regular and en bloc TDL should be further examined. Thereby one should take in consideration whether venous pressure was elevated and could be a possible underlying cause for the development of chylothorax, which role SP plays on venous pressure and probably even if this differs between both ligation techniques. Furthermore the impact of ligating the azygous vein is not known and is also thought to contribute to the changes in venous pressure.(MacDonald, Noble, and Burrow 2008) For evaluating all of this, ideally a blinded randomized study with large patient groups is needed.

A big part of patients with failure of treatment suffer from clinically persisting liquothorax with nonchylous effusion after surgery, the cause is still unknown. For example in the en bloc TDL study of Viehoff and Stokhof only 2 of 6 dogs with failure of treatment had a persistent chylothorax, suggesting that in the other 4 cases the thoracic duct was successfully ligated, but this was not enough to cure the effusion. Therefore it seems that treatment of chylothorax does sometimes need more than TDL only. (MacDonald, Noble, and Burrow 2008; Viehoff and Stokhof 2003) The ligation of the thoracic duct was probably successful because the aspect of chyle disappeared. Speculations are that the source of this remaining effusion is independent of the chylous portion of effusion and could be caused by chronic pleuritis for example. Or it could be lymph originating from the cranial body. When this lymph enters the mediastinum via the pulmonary lymphatics it could leak through other or still existing lymphangiectasis. (Allman et al. 2010; Fossum et al. 2004; McAnulty 2011; Singh 2012a; Viehoff and Stokhof 2003) A persistent liquothorax should therefore probably not be seen as a failure of TDL, but still is a failure in treating the patient because there are still health issues due to pleural effusion.(Mayhew et al. 2012; Viehoff and Stokhof 2003) The prognosis of patients with persisting liquothorax seems to be poor, attempts to drain the effusion with omentalization or active or passive pleurovenous drainage are mostly unsuccessful on long term. (Singh 2012a; Viehoff and Stokhof 2003)

The suggestion that inflammation of thoracic structures might have a role in the continuing effusion is further supported in the study of Mcanulty in 2011. Nonchylous pleural effusion was seen 3 to 6 weeks after surgery in 5 of 22 dogs in this study. The patients were treated with prednisone over an 1 to 1.5 month period. This seemed to work in 3 out of 5 cases.(McAnulty 2011) Prednisone could therefore be an option worth trying when persisted liquothorax exists after surgery. Furthermore, the origin from this remaining pleural effusion should be further researched so a more specific treatment protocol could be developed.

In the current study 2 dogs had persistent liquothorax after the first surgery and one other dog had a persistent chylothorax that turned into a persistent liquothorax after secondary surgery. Those three patients have, as far as known, not been treated with corticosteroids. One of this patients, number 11, had a secondary surgery performed with CCA and omentalization. This treatment did not resolve effusion. However there seems no strong rationale to perform CCA in patients with persisting liquothorax, since the aim of CCA is hindering chyle to reach the thoracic duct but there was no chyle leakage left in the patient.

Besides looking at treatment success of en bloc TDL and SP, the other aim of this study was comparing results after thoracotomy and thoracoscopy. Success for thoracoscopy was 60% and 50% for thoracotomy. When the 2 dogs, that received only en bloc TDL by thoracotomy, are excluded only 40% of thoracotomic surgeries turned out to be successful. This differences in success of thoracotomy in relation to thoracoscopy are, however, not significant. Which suggests that thoracoscopy indeed has a similar success rate as thoracotomy, as was expected. This is further supported by the survival analysis with a Kaplan Meier curve, that showed no significant difference for both treatments.

Furthermore, one of the claimed advantages of thoracoscopy over thoracotomy is reduced post-operative pain, especially in the period early after surgery.(Allman et al. 2010; Lyon et al. 2013; Walsh et al. 1999) In this period, up to 9 hours after surgery, Walsh et al. found significant higher pain scores, blood glucose and cortisol levels in dogs treated with thoracotomy.(Walsh et al. 1999) This component of recovery could not be described in this study, because all patients received different analgesics in different protocols after surgery and pain medication administered after leaving the clinic was not documented. Also no post-operative pain scores were determined. Therefore the hypothesis of reduced post-operative pain after thoracoscopy could not be confirmed nor rejected. To measure this, one should use a standardized analgesia protocol and a method for scoring post-operative pain in a further study. Furthermore one could

measure post-operative blood glucose and cortisol levels, which give indications of physiological stress experienced by the dogs. (Walsh et al. 1999)

Shorter hospitalization is another expected advantage of thoracoscopy due to its less invasive character. The difference between duration of hospitalization for both treatment groups in this study was only one day, in favor of thoracoscopy. Nevertheless the time of discharge was mostly depending on the moment the thorax drain could be removed and had less to do with pain management or wound morbidity. Which is probably the cause of the little difference. Furthermore as described earlier, the success rate of thoracoscopy found in the current study was similar to the success of thoracotomy and technically thoracoscopy seems to be a feasible technique for en bloc TDL and SP. Therefore thoracoscopy might in general be the more favorable option for surgical treatment of idiopathic chylothorax.

Weaknesses of this study are its retrospective character, and the small study groups, especially the group of cats (4 patients) and the group of thoracoscopic treated patients (5 patients). Findings like the low treatment success that contradict earlier studies, which moreover mostly have to cope with the same weaknesses, are therefore of unknown value. Thereby due to the retrospective approach of patient dossiers, not all information of interest was gathered during treatment at the clinic and there was no standardization of protocols for diagnosis and treatment. This makes comparison of patients difficult at some points. Further studies about chylothorax and its treatment, ideally with large randomized treatment groups and standardized protocols, are needed to confirm or reject suggested theories and differences between treatments and techniques.

One goal of this study was to evaluate en bloc TDL and SP as treatment of idiopathic chylothorax. The accomplished treatment success was lower than might be expected from previous studies. The reason of this finding is unknown. Extensive search for underlying causes, with special attention for restrictive pericardial problems, might be an important step diagnosis of disease and formulating the prognosis of treatment. Perhaps further research of the role of venous pressure and SP on chyle drainage and the newly formed drainage route after en bloc TDL could help the understanding of the etiology and treatment of idiopathic chylothorax. Also the origin of persistent nonchylous effusion after treatment should be investgated. Despite the results found in the current study, treatment with en bloc TDL and SP is still considered to be a good treatment option for patients with idiopathic chylothorax given other published results.

The other aim of research was to find out whether the outcomes after thoracoscopy and thoracotomy are similar. The success rates and mean survival time after surgery turned out to be similar. Furthermore thoracoscopy seems to be suitable for performing TDL and SP, although it prolongs surgery time and increase treatment costs. But on the other hand it seems to decrease hospitalization time and probably also reduces pain and morbidity due to invasive surgery. The need of specialized equipment and experience could make this procedure unsuitable for some clinics. One should therefore consider which factors are most important for the patient and the surgeon, but thoracoscopy might in general be preferred over thoracotomy as option for surgical treatment of idiopathic chylothorax.

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a. LigaSure™ vessel sealer/divider, monopolar tip, Covidien, Valleylab Inc, Boulder, Colorado.
b. Applied by UVDL (University Veterinary Diagnostic Laboratory)

Appendix

For an overview of diagnosis and treatment of chylothorax patients, see also the appendix of this report.

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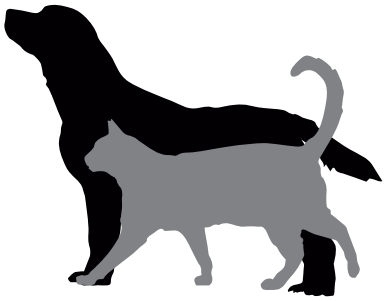
CHYLOTHORAX PATIENTS– Diagnosis and Treatment

appendix of: En bloc thoracic duct ligation and subtotal pericardectomy in dogs and cats with idiopathic chylothorax by thoracotomy versus thoracoscopy in 20 cases (2005-2013)

Patients [1,2]

Clinical signs: tachypnoea, dyspnoea, coughing, anorexia, weight loss, lethargy, decreased endurance.



Physical examination:

- Thorax auscultation: reduced heart and lung sounds in ventral thorax, increased lung sounds in dorsal thorax.
- Thorax percussion: dull sounds, exposes fluid line.

Diagnosis [1-4]

— Confirming chylous effusion; TG effusion > TG blood serum
TG effusion > 1.13 mmol/L [3]

— Further testing and medical imaging for underlying causes.
Echographic and radiographic examination, CT, biochemical and cytological testing.
This results in an idiopathic or non-idiopathic diagnosis, which require different treatment protocols.

Idiopathic
No underlying cause was found.

Non-idiopathic

- Trauma,
- Fungal granuloma,
- Thrombosis of cranial vena cava,
- Congentital abnormalities of TD,
- Obstruction of the thoracic duct,
- Lung lobe torsion,
- Diaphragmatic hernia,
- Mediastinal and pulmonary neoplasia,
- Cardiac or pericardial diseases.

Treatment [1-19]

Idiopathic

1. Medical treatment

Aim: relieving symptoms, support spontaneous thoracic duct healing.

⊕ not invasive, low costs,

⊖ Long-term medical treatment can result in hypoproteinemia, immunodeficiency, dehydration, weight loss, loss of necessary nutritional elements, extensive fibrosing pleuritis due to exposure to the irritating chyle.

When no clinical improvement is seen within 4 weeks or in high output effusions -> surgical treatment. [5]

Non-idopathic;

- Treatment of underlying cause.
- Relieving symptoms with medical treatment

2. Surgical treatment

Aim: Stop the leakage of chyle in the pleural space.

⊕ Higher chance of resolving of chylothorax than medical treatment.

⊖ higher costs, more invasive, surgical risks.

CHYLOTHORAX PATIENTS– Diagnosis and Treatment

Appendix of: En bloc thoracic duct ligation and subtotal pericardectomy in dogs and cats with idiopathic chylothorax by thoracotomy versus thoracoscopy in 20 cases (2005-2013)

Medical treatment [1,2,19]

	Thoracocentesis	Rutin administration
Aim	Delete chylous effusion from pleural space.	Exact mechanism of working unknown, working not proven yet.
⊕	Relieves patients respiratory distress.	Especially in cats clinical improvement is reported, no negative side effects are known.
⊖	Risk of causing infection and pneumothorax.	No guaranty for long term resolving of chylothorax.

Surgical treatment

Thoracic Duct Ligation (TDL)

Aim

Stop the chyle leakege from the thoracic duct and stimulation of formation of new lymphovenous connections by changed pressure in the lymphatic system after ligation.

- *Thoracoscopy (clipping or sealing) or thoracotomy,*
- *Single duct branches with lymphangiography or in en bloc fashion.*

Reported success:
cats ≤ 40%, dogs 50-60% [5-12]

	Thoracoscopy	*Thoracotomy*
⊕	Less invasive, excellent visualization due to magnification, shorter hospitalization, less post-operative pain.	Better overall vision, more room for handling.
⊖	Less overall vision (risk for damaging other structures), need for expertise and equipment.	More invasive, more post-operative pain, longer hospitalization, more wound morbidity.

[5,9,13,14,19]

Aditional Treatment

Subphrenic Pericardectomy (SP)

Aim

Decrease venous pressure at the right side of the heart and thereby facilitate the chyle excretion into the venous circulation.

- *With thoracotomy or thoracoscopy.*

⊕ In the same body cavity as thoracic duct ligation.

⊖ When performed with thoracoscopy patient rotation is needed, prolongs sugery time.

Reported success in combination with TDL:
60-100% (mean: 85%). [5,7-11]

Cisterna Chyli Ablation (CCA)

Aim

Remove the cisterna chyli, and thus disrupt the chyle flow into the thoracic duct and stimulate formation of new lymphovenous connections outside the thorax. Prevent hypertension in the lymphatic system caudal to ligation site of TD which could otherwise open patent collaterals.

- *With laparotomy, laparascopy or paracostal.*

⊕ When opening abdomen for lymphangiography it does not prolong surgery time very much when performed by a skilled surgeon.

⊖ Open another body cavity could give more pain and discomfort, incisional morbidity and longer anesthesia.

Reported success in combination with TDL:
67%-88% (mean: 79%). [15-18]

CHYLOTHORAX PATIENTS– Diagnosis and Treatment

Appendix of: En bloc thoracic duct ligation and subtotal pericardectomy in dogs and cats with idiopathic chylothorax by thoracotomy versus thoracoscopy in 20 cases (2005-2013)

Outcome [1,2,5,8-13,15-19]

Chylothorax resolved, no remaining clinical signs.

Remaining of clynical signs.
Analyse pleural fluid.

- Persistent Chylothorax
  - repeated TDL with lymphangiography or staining + other additional treatment (CCA or SP),
  - pleurovenous or pleuroperitoneal shunt,
  - Medical management.

- Persistent Liquothorax
  - Pleurovenous or pleuroperitoneal shunt,
  - Prednisone? [16]
  - Medical management.

Follow-up

At least 1 month after surgery:
Weekly radiography to monitor pleural effusion, until repeatedly stable condition is seen.

Long term follow-up:
> 20 months, to monitor recurrence of disease. [11]

Short references

[1] Singh 2012b
[2] Sturgess 2001
[3] Waddle 1990
[4] Fossum 2006
[5] Allman 2010
[6] Viehoff 2003
[7] Fossum 2004
[8] Carrobi 2008
[9] Mayhew 2012
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For the complete references see the accompanied report