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Effect of Intravenous Morphine Comedication on Bile Duct Visualization, Diameter and Volume Applying Intravenous CT Cholangiography in a Porcine Liver Model

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Key Words
Cholangiography · Computed tomography · Morphine · Biliscopin · Biliary system · Postprocessing

Abstract
Background/Aims: To determine whether intravenous morphine comedication improves bile duct visualization, diameter and/or volume applying intravenous CT cholangiography in a porcine liver model. ***Methods:*** 12 Landrace pigs underwent intravenous CT cholangiography. Eight minutes after initiation of the contrast material infusion, either morphine sulfate (n = 6 animals) or normal saline (n = 6 animals) was administered. Eighteen consecutive CT scans of the liver were acquired with 2-min intervals starting with initiation of the contrast material infusion. Maximum bile duct visualization scores, diameters and volumes and time to maximum bile duct visualization scores, diameters and volumes were determined. ***Results:*** Maximum bile duct visualization scores, diameters and volumes and time to maximum bile duct visualization scores, diameters and volumes were not significantly different when the morphine group was compared to the normal saline group. Maximum bile duct visualization scores ranged between 4.00 ± 0.00 and 2.83 ± 1.47. Maximum bile duct diameters ranged between 6.77 ± 0.40 and 2.10 ± 1.35 mm. Maximum bile duct volume was 16.41 ± 7.33 ml in the morphine group and 16.79 ± 5.65 ml in the normal saline group. ***Conclusion:*** Intravenous morphine comedication failed to improve bile duct visualization and to increase bile duct diameter and volume applying CT cholangiography.

Introduction

A conventional CT scan is not appropriate to provide imaging of the biliary tree with high quality [1]. However, detailed bile duct evaluation is essential in times of modern surgery such as living-related or cadaveric liver transplantation, atypical liver tumor resection or reconstruction of the biliary system [2–5]. The gold standard for the

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Table 1. Study groups

	Morphine group	p value	Normal saline group
Comedication	0.04 mg of morphine sulfate per kilogram of body weight		10 ml of normal saline
Animals, n	6		6
Body weight, kg	28.03 ± 1.06 (25.80–32.90)	n.s.	28.97 ± 2.99 (25.40–32.30)
Liver volume, ml	822.52 ± 181.74 (661.47–1,136.51)	n.s.	897.75 ± 203.98 (656.22–1,221.03)

Data is compared with the nonparametric Wilcoxon signed-rank test.

detection of biliary variations and pathologies is percutaneous transhepatic cholangiography with the possibility of therapeutic intervention [6, 7]. Endoscopic retrograde cholangiography allows delineation of the biliary tree with high spatial resolution; however, it is more difficult and dangerous in patients with modified anatomy as Billroth II gastrectomy or biliodigestive anastomosis [8]. Additionally, these invasive procedures lead to complications in up to 5% of cases [9]. Magnetic resonance cholangiography as a technique without irradiation is reliable for the identification of biliary stones, strictures and tumors [10–14]. Availability, costs, contraindications such as pacemakers and reduced image quality due to metallic clip artifacts or noncompliance make up its major limitations [9]. Intravenous administration of iodinated contrast materials with a biliary excretory profile in combination with a CT scan (CT cholangiography) has been reported to detect morphological and functional biliary pathologies with high sensitivity [15, 17]. Multidetector row CT scanners with modern postprocessing software provide fast data acquisition, and complex image reconstruction is feasible [1, 6, 17, 18]. While CT cholangiographic imaging of the extrahepatic biliary system is superb, exact delineation of higher-order bile ducts remains critical [9, 19]. Since variations and abnormalities occur particularly in second-order and third-order branch ducts, excellent visualization of these is mandatory [19–22]. The quality of bile duct opacification might be affected by the contrast material administration protocol. Longer-lasting and high-volume infusions with meglumine iotroxate seem to improve bile duct attenuation [23, 24]. Additionally, slow infusion is involved with reduced adverse contrast material reactions [17]. To further improve bile duct imaging, diverse pharmacological substances have been studied [25, 26]. In the context of cholescintigraphy, intravenous morphine premedication demonstrated improved hepatobiliary imaging [27–30]. Theoretically, morphine induces a spasm of the sphincter of Oddi with consecutive retention of gall and dilatation of the biliary system [26, 31–34]. Applying CT cholangiography, no report is published describing a positive effect of the premedication with morphine [19]. Therefore, we determined in this study whether intravenous morphine comedication improves bile duct visualization, diameter and volume applying CT cholangiography in a porcine liver model. Study goals included the evaluation of bile duct visualization scores, diameters and volumes for 18 consecutive CT scans of the liver acquired with 2-min intervals starting with initiation of the biliary contrast material infusion. Thereby, maximum values and time to maximum values were calculated.

Materials and Methods

In accordance with the Guide for the Care and Use of Laboratory Animals and after approval by our State Animal Care and Ethics Committee, 12 Landrace pigs underwent intravenous CT cholangiography [35]. The animals were equally divided into 2 study groups (table 1). In the morphine group, the biliary contrast material infusion was combined with a bolus injection of morphine sulfate (n = 6 animals). In the normal saline group, the biliary contrast material infusion was combined with a bolus injection of normal saline (n = 6 animals). The body weight was 28.03 ± 1.06 kg (range 25.80–32.90 kg) in the morphine group and 28.97 ± 2.99 kg (25.40–32.30 kg) in the normal saline group without significant differences. The liver volume, determined applying manual segmentation techniques as described before, measured 822.52 ± 181.74 ml (661.47–1,136.51 ml) in the morphine group and 897.75 ± 203.98 ml (656.22–1,221.03 ml) in the normal saline group without significant differences [36].

Animal Preparation and CT Cholangiography

The animals were sedated and intubated using standard techniques. General anesthesia was maintained with isoflurane and N_2O [26]. No additional medication for muscle relaxation was used [37]. A 4-french central venous catheter was positioned in the left internal jugular vein for the biliary contrast material administration. The animals were positioned head first in supine position in the CT gantry. As biliary contrast material, 50 ml of

Table 2. Bile duct visualization score

	Maximum bile duct visualization scores			Time to maximum bile duct visualization scores, min		
	morphine group	p value	normal saline group	morphine group	p value	normal saline group
Common duct	4.00 ± 0.00 (4.00–4.00)	n.s.	4.00 ± 0.00 (4.00–4.00)	5.67 ± 2.34 (2.00–8.00)	n.s.	7.67 ± 2.66 (6.00–12.00)
Cystic duct	3.50 ± 1.22 (1.00–4.00)	n.s.	2.83 ± 1.47 (1.00–4.00)	8.00 ± 6.81 (0.00–20.00)	n.s.	5.33 ± 4.50 (0.00–10.00)
First-order main ducts	4.00 ± 0.00 (4.00–4.00)	n.s.	4.00 ± 0.00 (4.00–4.00)	5.78 ± 2.72 (2.00–10.00)	n.s.	7.98 ± 3.21 (4.00–14.00)
Second-order branch ducts	3.84 ± 0.23 (3.50–4.00)	n.s.	3.92 ± 0.26 (3.50–4.00)	13.50 ± 7.94 (4.00–28.00)	n.s.	15.92 ± 6.51 (8.00–26.00)
Third-order branch ducts	3.34 ± 0.89 (2.50–4.00)	n.s.	3.42 ± 0.76 (2.50–4.00)	16.50 ± 9.42 (6.00–32.00)	n.s.	20.33 ± 10.65 (8.00–34.00)

Data is compared with the nonparametric Wilcoxon signed-rank test.

meglumine iotroxate were infused continuously over a period of 20 min [7]. Eight minutes after initiation of the biliary contrast material infusion, an intravenous bolus of either morphine sulfate (0.04 mg/kg body weight; Morphin Hexal®, Salutas Pharma GmbH, Barleben, Germany) in the morphine group or 10 ml of normal saline in the normal saline group was injected [19]. In each animal, 18 consecutive CT scans of the liver were obtained with 2-min intervals. The time point of the first scan was identical with the initiation of the biliary contrast material infusion. All scans were performed with a 64-multidetector-row CT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany). Scanning parameters included a tube potential of 120 kV, a tube current of 200–244 mAs/rotation, a gantry rotation time of 0.33–0.5 s, a detector configuration of 64 × 0.6 mm with a pitch of 0.5–0.7 and a field of view of 50 cm. Reconstructed image matrix size was 512 × 512 pixels. Axial image reconstruction was performed in a soft tissue window (center/width: 30 /400 Hounsfield units) with a medium soft body kernel (B45f). Reconstructed slice thickness was chosen to be 1 mm with a reconstruction increment of 0.5 mm.

Data Analysis

Two readers blinded to the study group reviewed in consensus the 18 CT scans in all animals. Bile duct visualization scores and diameters were analyzed on a picture archiving and communication system workstation (GE Centricity 4.1, GE Healthcare, Barrington, Ill., USA). Bile duct volumes were evaluated on a Terarecon workstation (Terarecon Inc., Aquarius, Intuition™ edition, version 4.4.1.6.1502, San Mateo, Calif., USA). The bile duct visualization scores were determined for the common duct, cystic duct, first-order main ducts, second-order branch ducts and third-order branch ducts [19]. Thereby, the bile ducts were graded on a 4-point scale: 1 = not visualized; 2 = faintly seen; 3 = identified, but the origin or portions of the duct are not visualized; 4 = excellent visualization [38]. The maximum bile duct visualization scores and the time to maximum bile duct visualization score were determined applying individual animal data. The bile duct diameters were determined for the common duct, cystic duct and first-order main ducts [19]. Thereby, the maximum short-axis diameters were measured as previously described [19]. The maximum bile duct diameters and the time to maximum bile duct diameters were determined applying individual animal data. The bile duct volume was determined applying the semiautomated segmentation component of the Terarecon workstation. Series were loaded in 'CTA abdomen' workflow (center/width: 30/400 Hounsfield units). Then, the attenuated bile ducts were segmented automatically using a region-growing algorithm. Starting from a seed point, a growing region was included applying the 'dynamic region growing tool' with 'auto' mode and 'tight' connectivity settings. Subsequent interactive adjustments such as multiple seed points in peripheral ducts were executed to include also higher-order branch ducts. The resulting segmented attenuated bile ducts underwent further processing that computes the complete bile duct volume and the bile duct volume without gallbladder/cystic duct. The maximum complete bile duct volume, the maximum bile duct volume without gallbladder/cystic duct, the time to maximum complete bile duct volume and the time to maximum bile duct volume without gallbladder/cystic duct were calculated applying individual animal data.

Statistical Analysis

All descriptive and comparative statistics were done with SAS software (version 9.1, SAS Institute Inc., Cary, N.C., USA). Data is presented as means ± SD and absolute value ranges. Comparative statistics was performed with the nonparametric Wilcoxon signed-rank test. $p < 0.05$ was considered as the level of statistical significance. The statistical analysis was recommended by the institutional consulting program.

Results

Bile Duct Visualization Scores

Maximum bile duct visualization scores of common, cystic and first-order main ducts as well as second-order and third-order branch ducts were not significantly different when the morphine group was compared to the normal saline group (table 2). The maximum bile duct visualization score of the common duct was 4.00 ± 0.00 (4.00–4.00) in the morphine group and in the normal saline group (table 2). The maximum bile duct visualization score of the cystic duct was 3.50 ± 1.22 (1.00–4.00) in the morphine group and 2.83 ± 1.47 (1.00–4.00) in the normal saline group. The maximum bile duct visualization

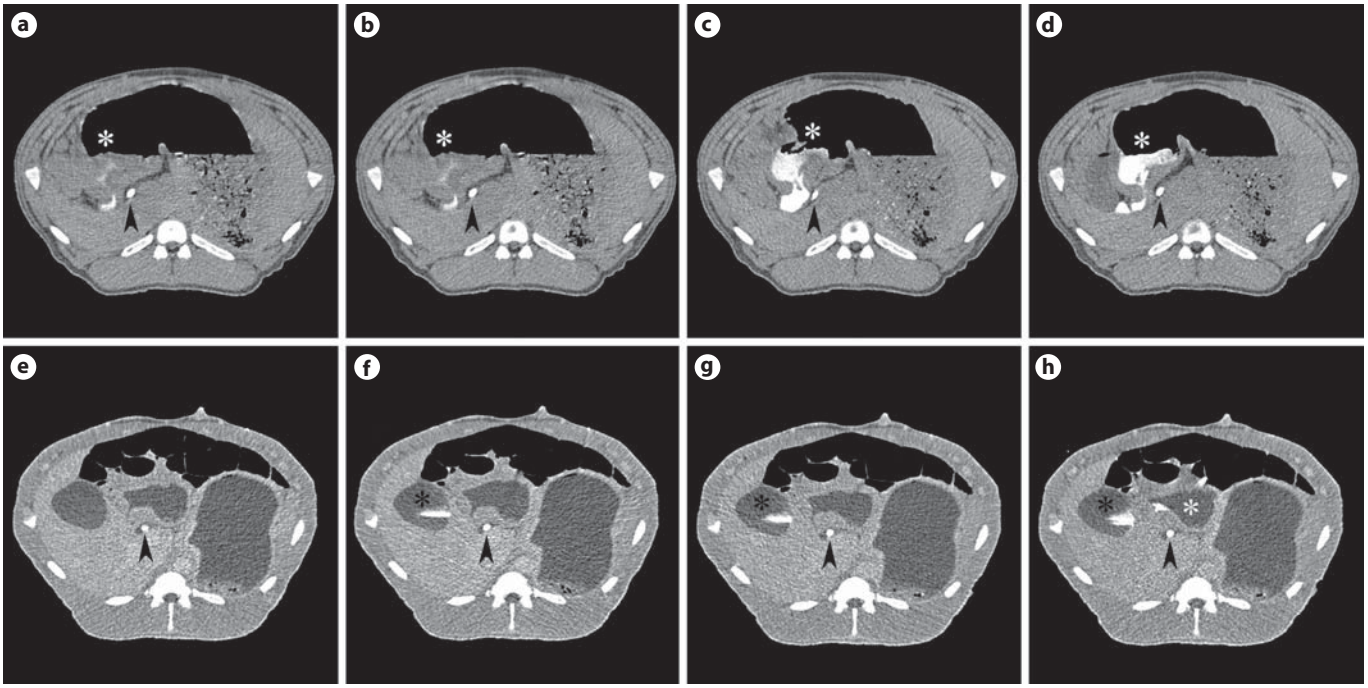

Fig. 1. Representative sequential axial images of the common duct (arrowheads), 8 min (**a**, **e**), 16 min (**b**, **f**), 24 min (**c**, **g**) and 32 min (**d**, **h**) after initiation of the intravenous biliary contrast agent infusion; good visualization and high diameter and attenuation for all time points without significant differences when the morphine group (**a–d**) was compared to the normal saline group (**e–h**); white asterisks indicate biliary contrast agent in the stomach and duodenum; black asterisks indicate biliary contrast agent in the gallbladder.

score of the first-order main ducts was 4.00 ± 0.00 (4.00–4.00) in the morphine group and in the normal saline group. The maximum bile duct visualization score of the second-order branch ducts was 3.84 ± 0.23 (3.50–4.00) in the morphine group and 3.92 ± 0.26 (3.50–4.00) in the normal saline group. The maximum bile duct visualization score of the third-order branch ducts was 3.34 ± 0.89 (2.50–4.00) in the morphine group and 3.42 ± 0.76 (2.50–4.00) in the normal saline group.

Times to maximum bile duct visualization scores of common, cystic and first-order main ducts as well as second-order and third-order branch ducts were not significantly different when the morphine group was compared to the normal saline group. Time to maximum bile duct visualization score of the common duct was 5.67 ± 2.34 min (2.00–8.00 min) in the morphine group and 7.67 ± 2.66 min (6.00–12.00 min) in the normal saline group. Time to maximum bile duct visualization score of the cystic duct was 8.00 ± 6.81 min (0.00–20.00 min) in the morphine group and 5.33 ± 4.50 min (0.00–10.00 min) in the normal saline group. Time to maximum bile duct visualization score of the first-order main ducts was 5.78 ± 2.72 min (2.00–10.00 min) in the morphine group and 7.98 ± 3.21 min (4.00–14.00 min) in the normal saline group. Time to maximum bile duct visualization score of the second-order branch ducts was 13.50 ± 7.94 min (4.00–28.00 min) in the morphine group and 15.92 ± 6.51 min (8.00–26.00 min) in the normal saline group. Time to maximum bile duct visualization score of the third-order branch ducts was 16.50 ± 9.42 min (6.00–32.00 min) in the morphine group and 20.33 ± 10.65 min (8.00–34.00 min) in the normal saline group. Thereby, no significant differences were detected when the morphine group was compared to the normal saline group.

Bile Duct Diameters

Maximum bile duct diameters of common (fig. 1), cystic and first-order main ducts (fig. 2) were not significantly different when the morphine group was compared to the normal saline group. The maximum bile duct diameter of the common duct was 5.58 ± 1.55 mm (3.30–8.00 mm) in the morphine group and 6.77 ± 0.40 mm (5.30–8.00 mm) in the normal saline group (table 3). The maximum bile duct diameter of the cystic duct was 2.10

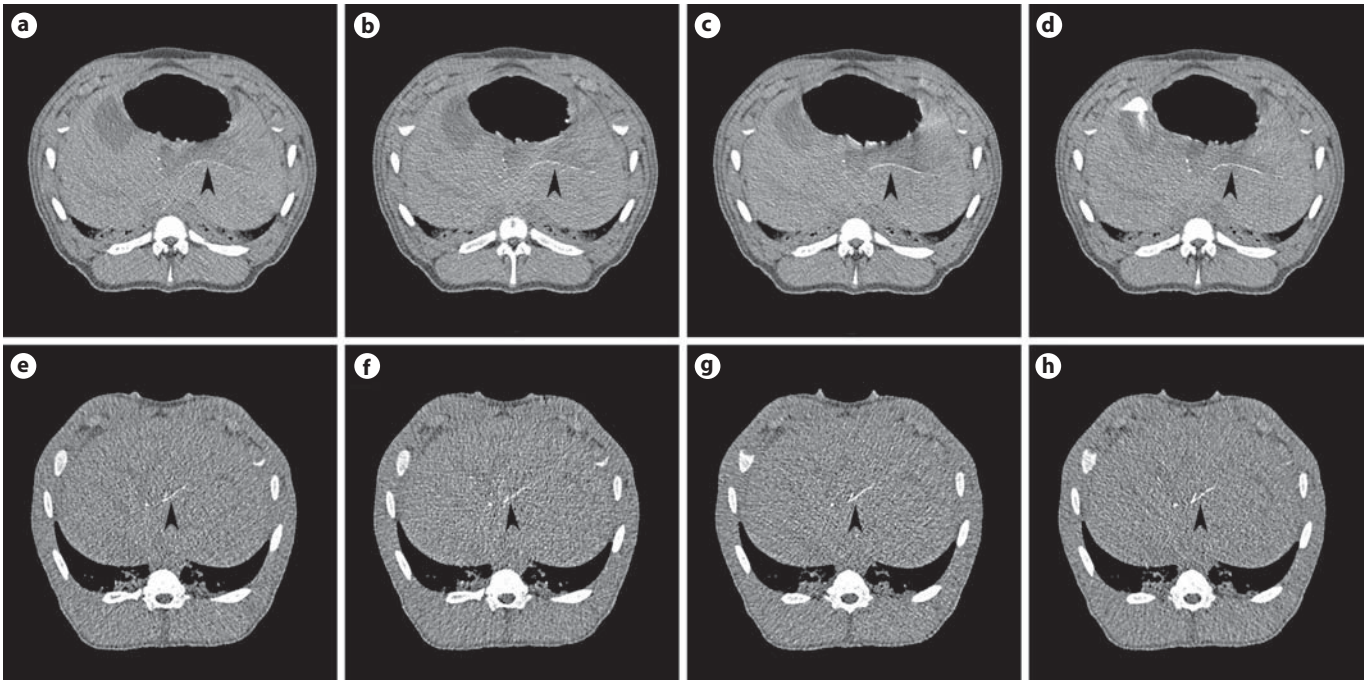

Fig. 2. Representative sequential axial images of a higher-order left branch duct (arrowheads), 8 min (**a**, **e**), 16 min (**b**, **f**), 24 min (**c**, **g**) and 32 min (**d**, **h**) after initiation of the intravenous biliary contrast agent infusion; clearly better visualization over time without significant differences when the morphine group (**a–d**) was compared to the normal saline group (**e–h**).

Table 3. Bile duct diameter

	Maximum bile duct diameters, mm			Time to maximum bile duct diameters, min		
	morphine group	p value	normal saline group	morphine group	p value	normal saline group
Common duct	5.58 ± 1.55 (3.30–8.00)	n.s.	6.77 ± 0.40 (5.30–8.00)	23.67 ± 11.55 (8.00–34.00)	n.s.	22.67 ± 8.73 (12.00–34.00)
Cystic duct	2.10 ± 1.35 (0.00–3.30)	n.s.	3.32 ± 1.99 (0.00–5.00)	16.40 ± 14.72 (0.00–34.00)	n.s.	15.60 ± 10.99 (0.00–28.00)
First-order main ducts	3.21 ± 1.13 (1.70–5.60)	n.s.	3.31 ± 0.91 (1.70–5.00)	20.84 ± 10.39 (6.00–34.00)	n.s.	18.00 ± 9.55 (6.00–34.00)

Data is compared with the nonparametric Wilcoxon signed-rank test.

± 1.35 mm (0.00–3.30 mm) in the morphine group and 3.32 ± 1.99 mm (0.00–5.00 mm) in the normal saline group. The maximum bile duct diameter of the first-order main duct was 3.21 ± 1.13 mm (1.70–5.60 mm) in the morphine group and 3.31 ± 0.91 mm (1.70–5.00 mm) in the normal saline group.

Times to maximum bile duct diameters of common, cystic and first-order main ducts were not significantly different when the morphine group was compared to the normal saline group. Time to maximum bile duct diameter of the common duct was 23.67 ± 11.55 min (8.00–34.00 min) in the morphine group and 22.67 ± 8.73 min (12.00–34.00 min) in the normal saline group. Time to maximum average bile duct caliber of the cystic duct was 16.40 ± 14.72 min (0.00–34.00 min) in the morphine group and 15.60 ± 10.99 min (0.00–28.00 min) in the normal saline group. Time to maximum bile duct diameter of the first-order main ducts was 20.84 ± 10.39 min (6.00–34.00 min) in the morphine group and 18.00 ± 9.55 min (6.00–34.00 min) in the normal saline group.

Bile Duct Volumes

Maximum complete bile duct volume and maximum bile duct volume without gallbladder/cystic duct (fig. 3)

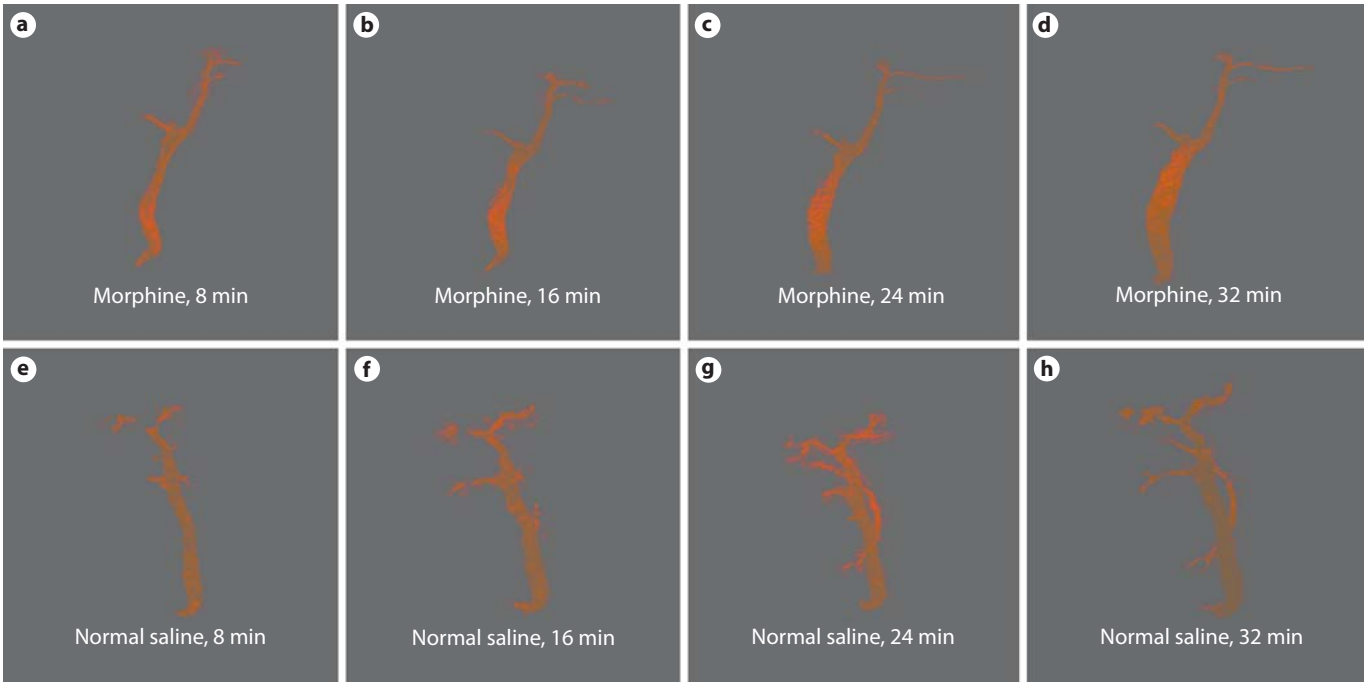

Fig. 3. Segmented bile duct volumes without gallbladder/cystic duct 8 min (**a**, **e**), 16 min (**b**, **f**), 24 min (**c**, **g**) and 32 min (**d**, **h**) after initiation of the intravenous biliary contrast agent infusion; clearly increasing bile duct volumes over time without significant differences when the morphine group (**a–d**) was compared to the normal saline group (**e–h**).

Table 4. Bile duct volume

	Morphine group	p value	Normal saline group
Maximum complete bile duct volume, ml	16.41 ± 7.33 (8.14–27.60)	n.s.	16.79 ± 5.65 (8.01–22.20)
Time to maximum complete bile duct volume, min	28.72 ± 2.32 (26.00–32.00)	n.s.	30.67 ± 5.32 (20.00–34.00)
Maximum bile duct volume without gallbladder/cystic duct, ml	10.73 ± 7.28 (4.60–23.20)	n.s.	14.24 ± 4.71 (8.01–19.90)
Time to maximum bile duct volume without gallbladder/cystic duct, min	27.60 ± 4.34 (22.00–32.00)	n.s.	29.33 ± 5.75 (22.00–34.00)

Data is compared with the nonparametric Wilcoxon signed-rank test.

were not significantly different when the morphine group was compared to the normal saline group (table 4). Maximum complete bile duct volume was 16.41 ± 7.33 ml in the morphine group and 16.79 ± 5.65 ml in the normal saline group. Maximum bile duct volume without gallbladder/cystic duct was 10.73 ± 7.28 ml in the morphine group and 14.24 ± 4.71 ml in the normal saline group.

Time to maximum complete bile duct volume and time to maximum bile duct volume without gallbladder/cystic duct were not significantly different when the morphine group was compared to the normal saline group. Time to maximum complete bile duct volume was 28.72 ± 2.32 min in the morphine group and 30.67 ± 5.32 min in the normal saline group. Time to maximum bile duct volume without gallbladder/cystic duct was 27.60 ± 4.34 min in the morphine group and 29.33 ± 5.75 min in the normal saline group.

Discussion

The excitatory effect of morphine on the sphincter of Oddi has been under investigation since the 1970s and has recently been verified by choledochoscope manom-

etry [39, 40]. Accordingly, morphine is able to increase basal pressure, frequency of phasic contractions and amplitude of phasic contractions of the sphincter of Oddi.

In our study, however, intravenous morphine comedication failed to improve bile duct visualization and to increase bile duct diameter and volume applying CT cholangiography in a porcine liver model. Furthermore, our examinations did not point out any significant differences in the time-dependent course regarding the time points at which the maximum bile duct visualization scores, diameters and volumes were achieved.

These results support the findings of Breiman et al. [19] recently publishing a scientific report on the effect of premedication with intravenous morphine sulfate in CT cholangiography in potential donors for living-related liver transplantation. Another biliary contrast material, iodipamide meglumine, was injected with a possibly different excretion profile compared to meglumine iotroxate [9]. Furthermore, Breiman et al. [19] used 20 ml of iodipamide meglumine diluted in 80 ml of normal saline, whereas in our study, 50 ml of pure meglumine iotroxate was injected. Additionally, the potential liver donors were premedicated with the intravenous bolus of morphine sulfate just prior to the start of a 30-min biliary contrast material application. Liver imaging followed 15 min after completion of the contrast material infusion. Thus, morphine was given 45 min prior to the CT scan. In our protocol, morphine was injected 8 min after initiation of the biliary contrast material infusion which equates 26 min prior to the last CT scan. Hence, we should have been able to observe the previously described prompt effects of intravenous morphine [25].

With our sequential CT scans over a 26-min postmorphine period, we should have been able to observe the established benefit of morphine as it was demonstrated with continued imaging in cholescintigraphy [27, 28, 30, 41]. We were however not able to demonstrate a similar effect of morphine during CT cholangiography. The reason for this discrepancy remains unclear. The iodinated biliary contrast material itself might cause a biliary widening so that morphine might have no substantial effect in this setting. In the future, CT cholangiography might be performed without the logistical hurdles linked with the use of a class 1 drug and without the potential side effects of morphine [19].

Since CT cholangiography is increasingly requested, modified biliary contrast material administration protocols and additional drugs, e.g. intravenous fentanyl citrate, should be evaluated to further improve CT cholangiography image quality [42].

There were limitations to our study. First, this investigation reflects our experiences in a small number of study animals. Second, the scientifically ideal study would have been to perform CT cholangiography on 2 different occasions in the same group of study animals, once with morphine and once without. However, logistic reasons made this impossible. Third, we evaluated only 1 infusion protocol for morphine, and we did not vary the timing of morphine administration relative to the administration of biliary contrast material. Of note, a single intravenous morphine bolus seems to be the most common method in cholescintigraphy, and we almost covered the 30-min interval used in cholescintigraphy. Additionally, we did not perform CT scans later than 34 min after initiation of contrast agent application. Subsequent CT scans might have led to different findings.

In this study, intravenous morphine comedication failed to improve bile duct visualization and to increase bile duct diameter and volume applying CT cholangiography in a porcine liver model.

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