Carbon Dioxide-Contrasted Computed Tomography Angiography: High Pitch Protocols and Adapted Injection Parameters Improve Imaging Quality

Kohlendioxid-kontrastierte computertomografische Angiografie: Protokolle mit hohem Pitch und angepassten Injektionsparametern verbessern die Bildqualität

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Key words
- CT angiography
- interventional procedures
- vascular
- experimental

Zusammenfassung

Ziel: Es sollen in einem klinisch zugelassenen Aufbau der Einfluss der Bildgebungs- und Injektionsparameter auf die computertomografische (CT) Kohlendioxid(CO_2)-kontrastierte Becken-Bein-Angiografie (CO_2-CTA) im Tiermodell untersucht werden. Ziel ist, ein Bildgebungsprotokoll zu etablieren, das für den Einsatz im Menschen geeignet ist.

Material und Methoden: In 3 Hausschweinen wurden CO_2-CTAs durchgeführt, wobei der Pitch (1,0, 3,0), der Injektionsdruck (0,7 bar, 1,0 bar, 1,3 bar) und die Scanverzögerung (2 s, 4 s, 6 s) systematisch variiert wurden. Objektive (Gefäßdurchmesser) und subjektive (Bildqualität) Kriterien sowie die applizierte Strahlendosis wurden evaluiert. Um eine klinische Einsetzbarkeit der entwickelten Protokolle zu gewährleisten, wurden nur zugelassene Interventionsmaterialien und Injektionsparameter untersucht.

Ergebnisse: Die Bildqualität war besser und die Gefäßdurchmesser größer, wenn Untersuchungsprotokolle mit hohem Pitch verwendet wurden (Durchmesser: 4,7 ± 2,0 mm gegenüber 3,6 ± 2,1 mm, p = 0,0040, Bildqualität (Skala von 1 – 4): 2,6 ± 1,1 vs. 2,0 ± 1,1, p = 0,0038). Höherer Injektionsdruck (1,3 bar) verbesserte ebenfalls die subjektiven und objektiven Bewertungsparameter (Gefäßdurchmesser: 3,6 ± 2,0 mm, 4,0 ± 2,1 mm und 4,6 ± 2,1 mm, jeweils für 0,7, 1,0 und 1,3 bar, p-Werte ≤ 0,0052, Bildqualität: 1,9 ± 1,1, 2,3 ± 1,1 und 2,7 ± 1,2, p-Werte ≤ 0,0017), ähnliches war für eine kürzere Scanverzögerung feststellbar (Durchmesser: 3,5 ± 2,0 mm, 4,2 ± 2,1 mm und 4,8 ± 2,1 mm, für 6 s, 4 s, und 2 s, p ≤ 0,0022, Bildqualität: 1,9 ± 1,1, 2,3 ± 1,1 und 2,7 ± 1,1, p-Werte ≤ 0,0013).

Schlussfolgerung: Höherer Pitch, kürzere Scanverzögerung und höherer Injektionsdruck verbessern die Bildqualität in der CO_2-CTA. Durch die Verwendung von zugelassenen Materialien ist das vorliegende Protokoll nun auf den Menschen übertragbar.

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Abstract

Purpose: To systematically investigate the impact of image acquisition and contrast injection parameters for CO_2-enhanced CT angiography (CTA) of the aorto-iliac and peripheral arteries in a pig model using commercially available equipment. The aim was to establish an imaging protocol that is ready for use in human subjects.

Materials and Methods: Three domestic swine underwent CO_2-CTA with varying injection parameters: pitch (1.0, 3.0), injection pressure (0.7 bar, 1.0 bar, 1.3 bar) and scan delay (2 s, 4 s, 6 s). Objective (vessel diameter) and subjective (image quality) parameters and applied radiation doses were systematically evaluated. To ensure clinical applicability of the setting, only approved catheters/injectors and standard injection parameters were evaluated.

Results: The image quality scores were superior and the vessel diameter was larger with high pitch in comparison to standard pitch (diameters: 4.7 ± 2.0 mm vs. 3.6 ± 2.1 mm, p = 0.0040, scores: 2.6 ± 1.1 vs. 2.0 ± 1.1, p = 0.0038). High injection pressure (1.3 bar) improved the image quality as assessed by subjective and objective ratings (diameters: 3.6 ± 2.0 mm, 4.0 ± 2.1 mm and 4.6 ± 2.1 mm, for 0.7, 1.0 and 1.3 bar, p-values ≤ 0.0052, scores: 1.9 ± 1.1, 2.3 ± 1.1 and 2.7 ± 1.2, p-values ≤ 0.0017), the same was observed for a shorter injection delay (diameters: 3.5 ± 2.0 mm, 4.2 ± 2.1 mm and 4.8 ± 2.1 mm, for 6 s, 4 s, and 2 s, p ≤ 0.0022, scores: 1.9 ± 1.1, 2.3 ± 1.1 and 2.7 ± 1.1, p-values ≤ 0.0013). The dose length products were 239 ± 47 mGycm (high pitch) and 565 ± 63 mGycm (standard pitch, p-values < 0.0001).

Conclusion: A higher pitch, shorter delay and higher injection pressure improve image quality in CO_2-enhanced CTA. Since commercially available, clinically approved equipment was used. The protocol is now ready for use in human subjects.

Introduction

With recent imaging technique and contrast agent developments, multi-slice computed tomography (CT) angiography (CTA) has become a standard diagnostic procedure for the noninvasive assessment of vascular pathologies [1 – 3] and has replaced catheter angiography for diagnostic purposes. The possibility of secondary post-processing and the availability of three-dimensional cross-sectional imaging further enhanced the diagnostic value of both methods in comparison to 2 D projectional imaging methods. The quantification and morphological analysis of the vasculature is facilitated, especially in the case of eccentric stenosis [4, 5]. Although still considered experimental, the possibility of plaque imaging is a promising tool to further adjust therapeutic options to the individual patient. Extravascular pathologies detected with cross-sectional imaging techniques add to their diagnostic value.

CTA, however, relies on iodinated contrast agents with potentially severe side effects such as allergy, induction of nephropathy or thyrotoxicity. As vascular imaging is frequently needed for the elderly and diabetic patients with an increased risk of impaired renal function, the application of iodinated contrast agents is frequently a high-risk endeavor. The other option, contrast-free time-of-flight magnetic resonance angiography (MRA), is considered to be contraindicated in the case of many of the currently available metal implants, such as many of the heart valves and most pacemakers, and is considered to be non-diagnostic in patients with stents, as are all commonly found in elderly patients with vascular pathologies. This makes it necessary to weigh the risk-benefit ratio between the need for a diagnosis and the patient's health.

Carbon dioxide (CO_2) is an established alternative to iodinated contrast agents in catheter angiography below the diaphragm [6]. It is a colorless, odorless and nonreactive gas, and even larger quantities are eliminated in a single pulmonary passage [7]. CO_2 does not affect kidney function and does not cause contrast-induced nephropathy. Apart from CT colonoscopy [8], where CO_2 is a well-established method of contrast, there are few reports of using carbon dioxide as a contrast agent for computed tomography examinations: uterine cavography [9], vesicography [10], depiction of the pulmonary arteries [11] and CT-guided aortic stent implantation [12].

In a previous proof of principle study [13], it has been shown that CO_2-enhanced CTA is possible in domestic pigs. However, in this study, CO_2 was injected by directly connecting the CO_2 bottle to the intra-arterial injection catheter. This procedure would be unacceptable in patients, in which case clinically approved CO_2 injectors have to be used. Moreover, bolus fragmentation and incomplete depiction of the vessel was an important limitation of CO_2-enhanced CTA in this previous study. We hypothesized that more advanced CT acquisition protocols such as high-pitch CT could help avoid such difficulties. High-pitch CT is a recent development in CT technology using the second X-ray source of a dual-source CT device to fill in sampling gaps, which would usually occur in single-source CT acquisitions, and a pitch value over 1.5 [14]. This allows for a CT table speed of up to 45 cm/s in CT scanners. However, faster bolus chasing with high-pitch CT requires an even more careful adjustment of the injection parameters and of the timing of injection and acquisition. Accordingly, the objective of this study was to systematically investigate the impact of different injection parameters and of the use of high-pitch CT on the image quality of CO_2-enhanced CTA of the aorta and run-off vessels with commercially available equipment for CO_2 angiography. The goal was to establish an optimized CO_2-CTA protocol for use in humans.

Materials and Methods

Animal Preparation

Three domestic swine (50 – 60 kg) were included in this study with the approval of the state committee on animal care. All examinations were performed under general anesthesia. After intramuscular pre-medication with 0.5 ml atropine 1 % (Atropinum sulfuricum solution 1 %, WDT, Garbsen, Germany), 2 mg/kg azaperone (Stresnil, Janssen-Cilag, Neuss, Germany), and 5 mg/kg body weight ketamine (ketamine 10 %, Ceva Tiergesundheit, Düsseldorf, Germany), anesthesia was induced by i. v. injection of 5 mg/kg body weight pentobarbital (Narcoren, Merial, Hallbergmoos, Germany). The animals were orotracheally intubated and mechanically ventilated throughout the entire procedure (Sulla 808, Draeger, Lübeck, Germany). Anesthesia was maintained with Isoflurane (Abbott, Baar, CH) with the goal of an end-tidal concentration of 1.0 % and continuous infusion of fentanyl (0.03 $mgkg^{-1}h^{-1}$; Janssen- Cilag, Neuss, Germany). After the completion of the experiments, the animals were sacrificed by an injection of pentobarbital (160 mg/kg body weight).

The animals were examined in the prone position with slightly elevated legs. Due to the comparably small vessel size of the foreleg arteries, instead of a brachial approach, an introducer sheath (Terumo Europe, Leuven, Belgium) was placed surgically in the right carotid artery to provide an antegrade access to the abdominal aorta. A 5F pigtail catheter with a radiopaque tip was introduced via the introducer sheath to the level of the infrarenal aorta and the position was confirmed using CT. A standard CO_2 injection set (CO_2 Angioset, OptiMed GmbH, Ettlingen, Germany) [15] filled with medical grade CO_2 (Linde AG, Germany) was used for all injections. The injection system consists of a 100 ml syringe and two pressure-resistant connection tubes. All injections were performed using a 100 ml injection volume as recommended by the vendor for aortic CO_2 injections. Prior to connection, the system was repeatedly flushed with CO_2 at least four times to remove any room air contamination.

CO_2-CTA Protocol

All animals underwent CO_2-enhanced dual-source CTA (DSCT) (SOMATOM Definition, Siemens, Forchheim, Germany) angiography with systematic variation of 3 different parameters:

- Pitch: 1.0 and 3.0,
- Injection pressure: 0.7 bar, 1.0 bar and 1.3 bar,
- Injection delay: 2 s, 4 s and 6 s.

All CO_2-CTA scans were repeated three times. With all parameter permutations, this resulted in a total number of 54 CO_2-enhanced CTA runs per animal. This setup allows intra- and inter-individual comparison of the influence of each of the different scan parameters on image quality. The scan order was randomized to minimize systematic confounders. The waiting time between two scans was at least two minutes as recommended for CO_2 injections [16].

All other CT acquisition parameters were kept stable between different runs of the same animal and across all three animals and were chosen as follows: collimation 2 × 32 × 0.6 mm, tube voltage 120 kV, tube current 120 mAs_{eff}. Images were reconstructed using a field-of-view of 226 × 226 mm, with a matrix of 512 × 512 using a

medium smooth convolution kernel (B30f) at a slice thickness of 1.0 mm with a 0.7 mm increment. The CO_2 injections and the CT scans were initiated synchronously from within the scanner room. Scan delays were achieved with the CT scanners scan delay function. The dose length products (DLP) were recorded and compared.

Data Analysis

All datasets were evaluated using objective and subjective criteria. The achieved vessel diameter was used as an objective criterion and was measured for the following vessels: aorta (AO), common iliac artery (CIA), internal iliac artery (IIA), external iliac artery (EIA), common femoral artery (CFA), superficial femoral artery (SFA), profound femoral artery (PFA) and popliteal artery (PA). The vessel diameters were measured four times for each territory by equidistantly dividing the respective territory into three parts and were then averaged. The subjective data analysis was performed using the Virtual Rendering Technique (VRT, lung preset, Siemens Leonardo, Siemens Healthcare, Forchheim, Germany) to judge the image quality on a 4-point scale (1 – non diagnostic: vessel anatomy was not depicted, 2 – diagnostic: vessels were sufficiently depicted with minor restrictions, 3 – good: vessels and collaterals were well depicted, 4 – excellent: main and up to second order collaterals were depicted surpassing the necessary diagnostic quality). As no dedicated VRT modes for solid reconstruction of a negative vascular contrast was available for medical image reconstruction, the imagery was also post-processed with dedicated segmentation software (MIMICS 14, Materialise, Leuven, Belgium). Dynamic region growing using Mimics (seeding point at 1000 HU, Min 50 HU, max 400 HU, with cavity fill) and 3 D model generation were applied (**Fig. 1**).

Data are presented as mean ± standard deviation (SD). To assess the association between pitch, pressure and delay, a repeated measures ANOVA was fitted to the data. The model included pitch (2 levels), pressure (3 levels), delay (3 levels) and vessel territories (8 levels), as well as two- and three-factor interactions. Suitable contrasts were formulated to test differences between selected pairs of injection/protocol settings. Dose-length products for high pitch and standard pitch were compared by means of t-test. All tests were two-sided and assessed at the 5 % significance level. Because of the exploratory character of the study, no adjustments were made to the significance level to account for multiple tests. Additional comparisons were carried out using Student's t-tests, also with a significance level of 5 %. All statistical analyses were performed using SAS® statistical software, V9.2 (SAS Institute, Cary, NC, USA).

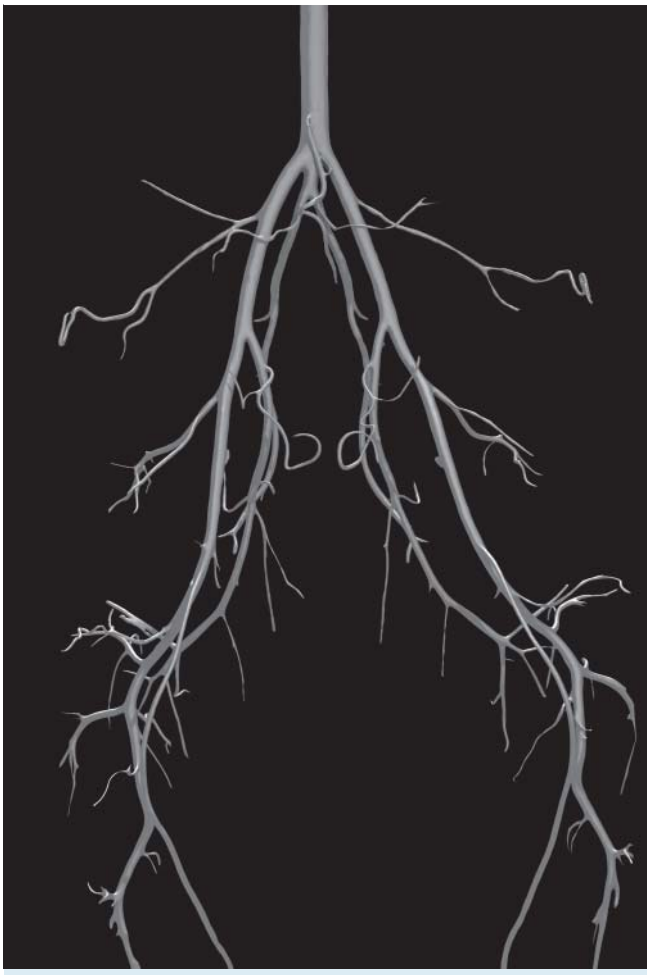

Fig. 1 Rendering based on segmented image data from a high-pitch, short-delay and high-pressure scan of the aorta and iliofemoral arterial territory (Mimics and Blender).

Abb. 1 Grafik der aortofemoralen Strombahn, basierend auf einer Bildsegmentierung eines Bilddatensatzes, der mit hohem Pitch, kurzem Delay und hohem Injektionsdruck durchgeführt wurde (Mimics und Blender).

Results

All CO_2 CT angiographies were successfully completed without any complications or adverse reactions.

Scan Parameters

The vessel diameters were larger when the scans were performed using the high-pitch scan mode in comparison to the standard-pitch protocol (4.7 ± 2.0 mm vs. 3.6 ± 2.1 mm, p = 0.0040), and the visual scores were higher (2.6 ± 1.1 vs. 2.0 ± 1.1, p = 0.0038). Both differences were statistically significant (**Fig. 2, 5**).

For the three injection pressure levels (0.7 bar, 1.0 bar and 1.3 bar), a higher injection pressure resulted in larger vessel diameters (3.6 ± 2.0 mm, 4.0 ± 2.1 mm and 4.6 ± 2.1 mm, for 0.7, 1.0

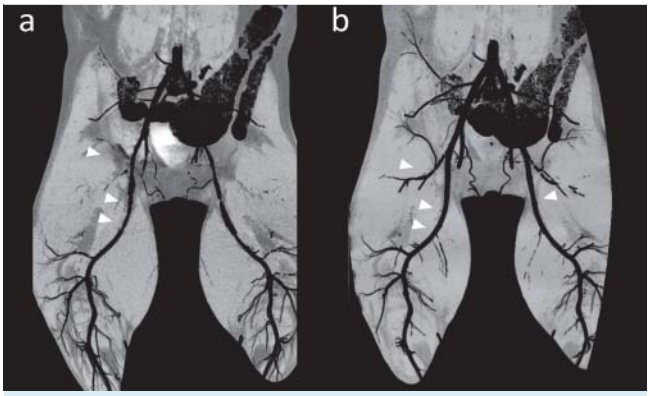

Fig. 2 Standard (1.0, left) versus high pitch (3.0, right) CO_2 CT angiography. High pitch yields a more expanded depiction of the vessels as compared to the standard pitch examination (arrowheads).

Abb. 2 Standard- (links, 1,0) und Hoch-Pitchaufnahme (rechts, 3,0) einer CT-CO_2-Angiografie. Der höhere Pitch führt zu einer erweiterten Darstellung der Gefäße im Vergleich zur Standard-Pitch-Aufnahme (Pfeilspitzen).

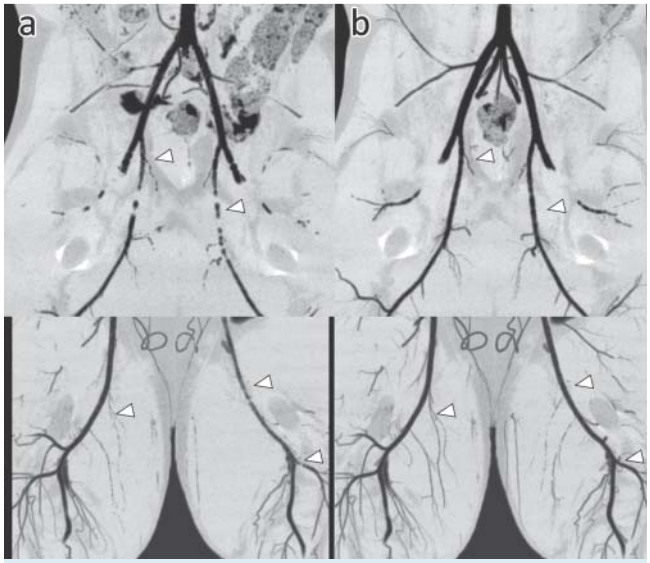

Fig. 3 Comparison of low (0.6 bar, left) to high (1.3 bar, right) injection pressure for proximal (upper half) and distal (lower half) vessel territories. A larger and smoother depiction of the arterial vessels can be observed with no bolus fragmentation in the main vessels (arrowheads) and only a slight irregularity of the vessel walls.

Abb. 3 Vergleich von niedrigem (0,6 bar, links) und hohem (1,3 bar, rechts) Injektionsdruck für die proximalen (oben) und distalen (unten) Gefäßabschnitte. In der Aufnahme mit dem höheren Injektionsdruck ist eine weitere und glattere Darstellung der Arterien erkennbar, ohne Bolusfragmentierung in den Hauptgefäßen, nur eine leichte Irregularität der Darstellung der Gefäße ist auszumachen.

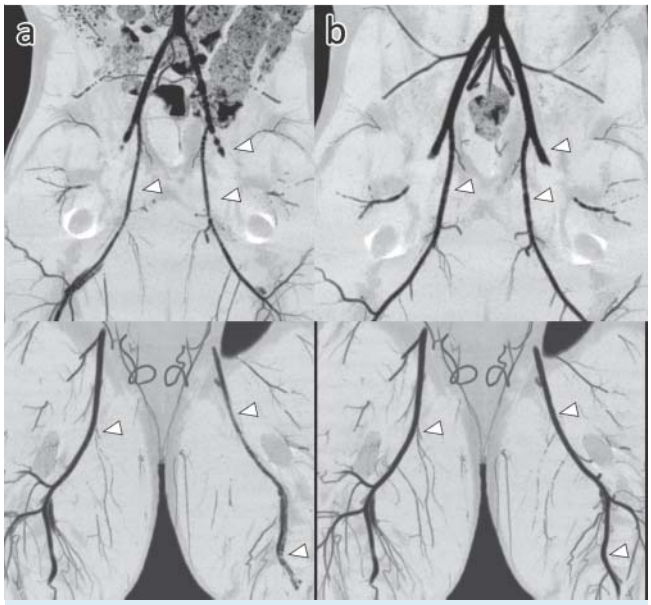

Fig. 4 Long (6 s, left) and short (2 s, right) delay CO_2 CTA for proximal (upper half) and distal (lower half) vessel territories. Less bolus fragmentation, only slight irregularities and larger depiction of the vessels are apparent with a shorter delay (arrowheads).

Abb. 4 Lange (6 s, links) und kurze (2 s, rechts) Scanverzögerung der CT-CO_2¬-Angiografie im Vergleich für die proximalen (oben) und distalen (unten) Gefäßabschnitte. Bei kurzem Delay zeigen sich eine geringere Bolusfragmentierung, nur eine geringe Unregelmäßigkeit der Wanddarstellung und weitere Gefäße (Pfeilspitzen).

Table 1 Summarized statistical results for the study per scan/injection parameter for subjective and objective measurements. Statistically significant testing is indicated by an asterisk (*, $p < 0.05$).

Tab. 1 Zusammengefasste statistische Ergebnisse getrennt nach Bildgebungs-/Injektionsparameter für die subjektiven und objektiven Messungen. Statistisch signifikante Unterschiede sind mit einem Stern markiert (*, $p < 0,05$).

		score	p-value	diameter [mm]	p-value
pitch	standard (1.0)	2.0 ± 1.1	*0.0038**	3.6 ± 2.1	*0.0040**
	high (3.0)	2.6 ± 1.1		4.7 ± 2.0	
pressure	0.6 bar	1.9 ± 1.1	*0.0017**	3.6 ± 2.0	*0.0052**
	1.0 bar	2.3 ± 1.1	*0.0001**	4.0 ± 2.1	*0.0009**
	1.3 bar	2.7 ± 1.2		4.8 ± 2.1	
delay	6 s	1.9 ± 1.1	*0.0010**	3.5 ± 2.0	*0.0010**
	4 s	2.3 ± 1.1	*0.0013**	4.2 ± 2.1	*0.0022**
	2 s	2.7 ± 1.1		4.8 ± 2.1	

and 1.3 bar, respectively, $p \leq 0.0052$ for all pair-wise comparisons). Moreover, the visual analysis yielded significantly higher image quality scores for higher injection pressures (1.9 ± 1.1, 2.3 ± 1.1 and 2.7 ± 1.2, p-values ≤ 0.0017 for all pair-wise comparisons) (**Fig. 3, 5**). A shorter injection delay also improved the image quality as revealed by larger vessel diameters (3.5 ± 2.0 mm, 4.2 ± 2.1 mm and 4.8 ± 2.1 mm, for 6 s, 4 s, and 2 s, respectively, p-values ≤ 0.0022) and higher scores (1.9 ± 1.1, 2.3 ± 1.1 and 2.7 ± 1.1, p-values ≤ 0.0013) (**Fig. 4, 5**, **Table 1**).

Injection Parameter Influence on Different Vascular Regions

All averaged vessel diameters and image quality scores were higher for high-pitch scanning (**Fig. 5**). This difference was statistically significant (p-values ≤ 0.0014) for all vascular regions except the subjective image quality of the aorta ($p = 0.1523$) and common iliac artery ($p = 0.1106$). A higher injection pressure led to higher image quality scores in all vessel territories (**Fig. 5**) with a statistically significant difference (p-values ≤ 0.0054, comparison 1.0 bar to 1.3 bar) in all but the common iliac territory (subjective, $p = 0.1335$). A shorter delay also had a positive influence on both vessel diameter and image quality (**Fig. 5**). For all territories a significant improvement in image quality and vessel diameter could be seen (p-values ≤ 0.028), with the exception of the subjective image quality of IIA and PA ($p = 0.1997$) (**Table 2 – 4**).

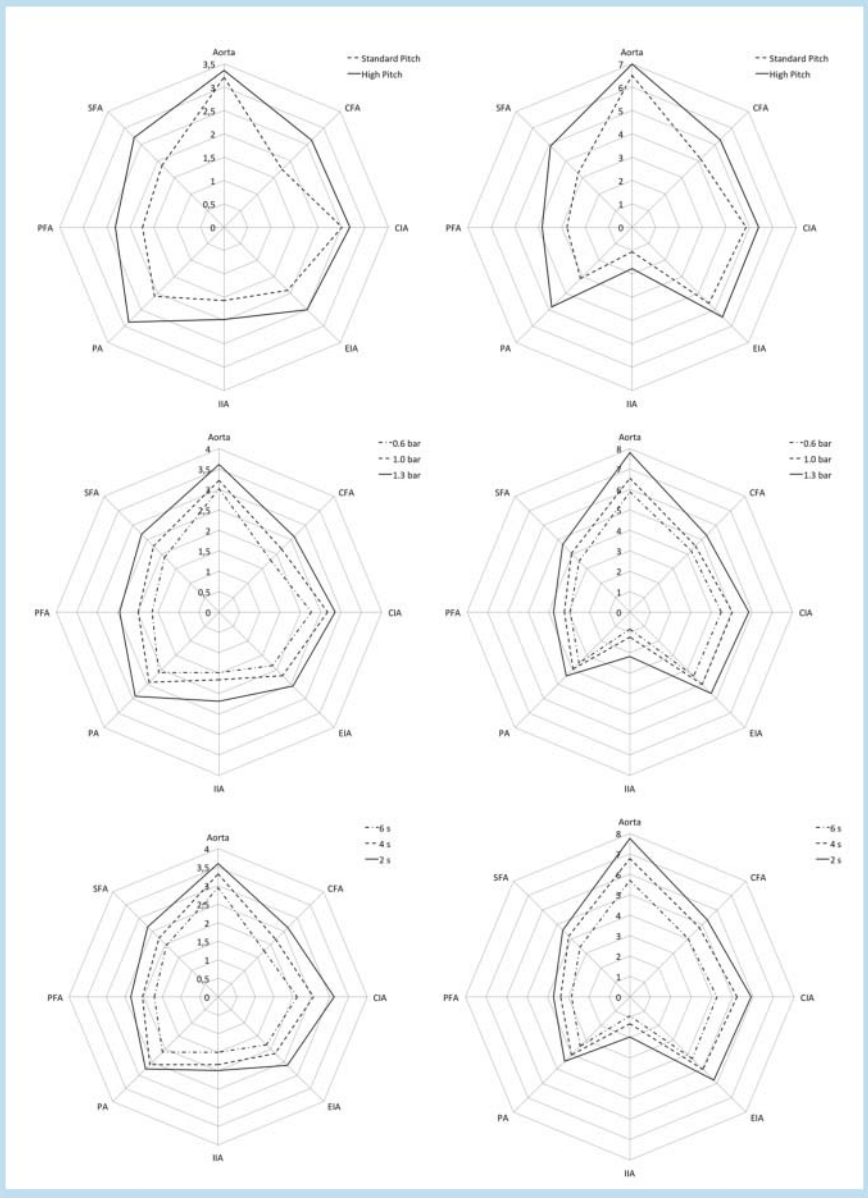

Fig. 5 Polar plots of the averaged results of different settings. Top row: A comparison of high-pitch scanning and standard-pitch scanning shows superiority of high-pitch scanning with respect to image quality (left) and vessel filling (right). Middle row: Better subjective (left) and objective (right) image quality for higher injection pressures is shown. Bottom row: Shorter delay leads to better image quality (left) and greater vessel diameters (right). Abbreviations: CFA: common femoral artery, CIA: common iliac artery, EIA: external iliac artery, IIA: internal iliac artery, PA: popliteal artery, PFA: profound femoral artery, SFA: superficial femoral artery.

Abb. 5 Polardiagramme der durchschnittlichen Ergebnisse der verschiedenen Einstellungen. Obere Zeile: Hoher gegenüber Standard-Pitch zeigt einen Vorteil der ersteren Einstellung in Bezug auf Bildqualität (links) und Gefäßdurchmesser (rechts). Mittlere Zeile: Bessere subjektive (links) und objektive (rechts) Bildqualität kann bei höherem Gefäßdruck erreicht werden. Untere Zeile: Eine kürzere Scanverzögerung führt zu besserer Bildqualität und größeren Gefäßdurchmessern. Abkürzungen: CFA: A. femoralis communis, CIA: A. iliaca communis, EIA: A. iliaca externa, IIA: A. iliaca interna, PA: A. poplitea, PFA: A. femoralis profunda, SFA: A. femoralis superficialis.

Dose Considerations

The DLP for high pitch and standard pitch was 239 ± 47 mGycm and 565 ± 63 mGycm, respectively. This difference was statistically significant at $p < 0.0001$.

Multiple Cross Comparison

Comparing all combinatory pairs of injection/protocol settings revealed a significant difference between high pitch/short delay/high pressure (pitch 3.0, delay 2 s, pressure 1.3 bar) over the remaining settings (all comparisons $p < 0.05$) with the exception of a non-significant difference of the achieved score in the high-pitch scenario for 1.0 bar vs. 1.3 bar with a 2 s delay ($p = 0.4310$).

Discussion

CO_2 is an established contrast agent for diagnostic angiography. Its main advantages include the lack of nephrotoxic, thyrotoxic and allergenic potential [7]. The feasibility of using CO_2 as a contrast agent for CTA has recently been shown in an animal model [13]. However, the materials used for this animal study were not in accordance with approved medical procedures. Thus, the results were not acceptable for human use. Moreover, in a previous study image quality and therefore vessel visualization were still limited [13]. Derived from the experience with CO_2 DSA, it can be hypothesized that the common problems limiting vessel visualization in CO_2-CTA are mistiming of the CO_2 bolus and the CT scan position, resulting CT imaging at the positions of bolus fragmentation and ultimately low vessel filling. To date, there are no clinically approved means for improving the homogeneity of the CO_2 bolus and for avoiding bolus fragmentation. In the initial animal study this was achieved by connecting the CO_2 source directly to the catheter in order to permit prolonged gas insufflation. However, this has important safety concerns including the insufflation of large amounts of gas. This may cause pain due to prolonged ischemia, with CO_2 displacing the blood. In addition, a large amount of gas may affect gas exchange, as CO_2 is eliminated via the respiratory system. Finally, this approach is not approved for human use. Therefore, in this study we used approved means of gas insufflation in order to overcome these safety concerns.

Table 2 Comparison of high-pitch versus standard-pitch scanning in different vessel territories. All territories but the aortic and common iliac vessels were improved with respect to diameter and image quality by high-pitch scanning (CIA: common iliac artery, IIA: internal iliac artery, EIA: external iliac artery, CFA: common femoral artery, SFA: superficial femoral artery, PFA: profound femoral artery, PA: popliteal artery). Statistically significant testing is indicated by an asterisk (*, $p < 0.05$).

Tab. 2 Vergleich von hohem gegenüber Standard-Pitch für unterschiedliche Gefäßterritorien. Bei allen Gefäßterritorien außer der Aorta und der A. iliaca communis wurden die Gefäßdurchmesser und die Bildqualität durch hohen Pitch signifikant verbessert (CFA: A. femoralis communis, CIA: A. iliaca communis, EIA: A. iliaca externa, IIA: A. iliaca interna, PA: A. poplitea, PFA: A. femoralis profunda, SFA: A. femoralis superficialis). Statistisch signifikante Unterschiede sind mit einem Stern markiert (*, $p < 0{,}05$).

		standard pitch	p-value	high pitch
Aorta	Diameter [mm]	6.5 ± 2.1	*0.0014**	7.0 ± 2.0
	Score	3.2 ± 0.6	*0.1523*	3.4 ± 0.7
CFA	Diameter [mm]	4.1 ± 1.6	*< 0.0001**	5.3 ± 1.4
	Score	1.7 ± 1.1	*< 0.0001**	2.6 ± 1.1
CIA	diameter [mm]	4.9 ± 1.7	*0.0007**	5.4 ± 1.7
	score	2.5 ± 1.0	*0.1106*	2.7 ± 1.0
EIA	diameter [mm]	4.6 ± 1.5	*< 0.0001**	5.4 ± 1.4
	score	1.9 ± 1.0	*< 0.0001**	2.5 ± 1.1
IIA	diameter [mm]	1.1 ± 1.5	*< 0.0001**	1.8 ± 1.7
	score	1.6 ± 0.9	*0.0011**	2.0 ± 1.1
PA	diameter [mm]	3.1 ± 1.6	*< 0.0001**	4.8 ± 0.8
	score	2.1 ± 1.2	*< 0.0001**	2.9 ± 1.2
PFA	diameter [mm]	2.8 ± 1.6	*< 0.0001**	3.8 ± 1.2
	score	1.7 ± 1.1	*< 0.0001**	2.3 ± 1.1
SFA	diameter [mm]	3.3 ± 1.7	*< 0.0001**	4.9 ± 1.1
	score	1.9 ± 1.1	*< 0.0001**	2.7 ± 1.2

Table 3 Comparison of different injection pressure settings separated by vessel territory. In all cases a higher injection pressure was statistically significantly beneficial with respect to image quality and vessel diameter. Statistically significant values are marked with an asterisk (*, $p < 0.05$) (AO: aorta, CIA: common iliac artery, IIA: internal iliac artery, EIA: external iliac artery, CFA: common femoral artery, SFA: superficial femoral artery, PFA: profound femoral artery, PA: popliteal artery).

Tab. 3 Vergleich verschiedener Injektionsdrücke pro Gefäßterritorium. In allen Fällen hat ein höherer Injektionsdruck zu einer statistisch signifikanten Verbesserung der Bildqualität und der Gefäßdurchmesser geführt. Statistisch signifikante Unterschiede sind mit einem Stern markiert (*, $p < 0{,}05$) (CFA: A. femoralis communis, CIA: A. iliaca communis, EIA: A. iliaca externa, IIA: A. iliaca interna, PA: A. poplitea, PFA: A. femoralis profunda, SFA: A. femoralis superficialis).

		0.6 bar	p-value	1 bar	p-value	1.3 bar
aorta	diameter [mm]	5.9 ± 1.7	*< 0.0001**	6.6 ± 1.9	*< 0.0001**	7.8 ± 2.1
	score	3.0 ± 0.6	*0.0001**	3.2 ± 0.6	*0.0030**	3.6 ± 0.6
CFA	diameter [mm]	4.3 ± 1.5	*0.0030**	4.6 ± 1.5	*< 0.0001**	5.3 ± 1.6
	score	1.8 ± 1.0	*0.0457**	2.2 ± 1.1	*0.0011**	2.6 ± 1.1
CIA	diameter [mm]	4.5 ± 1.7	*0.0025**	5.0 ± 1.5	*< 0.0001**	5.8 ± 1.7
	score	2.3 ± 1.0	*0.0013**	2.7 ± 0.9	*0.1335*	2.9 ± 1.0
EIA	diameter [mm]	4.4 ± 1.4	*0.0066**	5.0 ± 1.4	*0.0003**	5.6 ± 1.5
	score	1.9 ± 1.0	*0.0006**	2.2 ± 1.0	*0.0054**	2.6 ± 1.1
IIA	diameter [mm]	0.8 ± 1.1	*0.1533*	1.2 ± 1.5	*< 0.0001**	2.2 ± 1.9
	score	1.5 ± 0.8	*0.0170**	1.7 ± 1.0	*0.0001**	2.2 ± 1.2
PA	diameter [mm]	3.5 ± 1.7	*0.0096**	4.0 ± 1.5	*0.0039**	4.4 ± 1.3
	score	2.1 ± 1.2	*0.0101**	2.4 ± 1.2	*0.0004**	2.9 ± 1.2
PFA	diameter [mm]	2.9 ± 1.5	*0.0079**	3.2 ± 1.5	*0.0016**	3.8 ± 1.4
	score	1.6 ± 0.9	*0.0597*	2.0 ± 1.1	*0.0007**	2.4 ± 1.1
SFA	diameter [mm]	3.5 ± 1.7	*0.0037**	4.1 ± 1.6	*0.0004**	4.7 ± 1.5
	score	1.9 ± 1.1	*0.0014**	2.3 ± 1.3	*0.0017**	2.7 ± 1.2

Another means of overcoming the limitations of the previous study on CO_2-CTA with the aim of improved image quality was to increase the CT table feed by applying high-pitch CT protocols. The idea was to follow the CO_2 bolus in a more reliable manner as it advances in the vasculature. High-pitch scanning is achieved with scanners with two X-ray sources, effectively reducing the rotation angle needed for image generation to one fourth of a rotation. This reduction can be exploited to accomplish pitch values of up to 3.4 at table feeds of up to 450 mm/s [14]. However, high-pitch scanning may result in outpacing of the contrast bolus. This might be a problem in the presence of flow-limiting vascular lesions. Additional studies with different pitch values might improve imaging quality even further.

Our results prove the benefit of high-pitch scan protocols over standard-pitch scan protocols. High-pitch protocols revealed significantly better subjective image quality. Furthermore, the vessel diameters, an objective indicator for good distension of the target vessels, were significantly larger for the high-pitch proto-

Table 4 Comparison of injection delay settings separated by vessel territory. In all but the internal iliac and the popliteal vessel territories a shorter delay significantly improved the image quality and vessel diameter. Statistically significant values are marked with an asterisk (*, $p < 0.05$) (CIA: common iliac artery, IIA: internal iliac artery, EIA: external iliac artery, CFA: common femoral artery, SFA: superficial femoral artery, PFA: profound femoral artery, PA: popliteal artery).

Tab. 4 Vergleich der Ergebnisse für die verschiedenen untersuchten Injektionsverzögerungen. In allen Territorien außer der A. iliaca interna und der A. poplitea wurden die Ergebnisse durch eine kürzere Verzögerung verbessert. Statistisch signifikante Unterschiede sind mit einem Stern markiert (*, $p < 0{,}05$). (CFA: A. femoralis communis, CIA: A. iliaca communis, EIA: A. iliaca externa, IIA: A. iliaca interna, PA: A. poplitea, PFA: A. femoralis profunda, SFA: A. femoralis superficialis).

		6 s	p-value	4 s	p-value	2 s
Aorta	diameter [mm]	5.7 ± 1.7	*< 0.0001**	6.8 ± 1.8	*< 0.0001**	7.8 ± 2.0
	score	2.9 ± 0.6	*0.0045**	3.3 ± 0.6	*0.0280**	3.6 ± 0.5
CFA	diameter [mm]	4 ± 1.6	*< 0.0001**	4.8 ± 1.5	*0.0015**	5.3 ± 1.5
	score	1.8 ± 1.0	*0.0011**	2.2 ± 1.1	*0.0007**	2.6 ± 1.1
CIA	diameter [mm]	4.2 ± 1.8	*< 0.0001**	5.2 ± 1.5	*< 0.0001**	5.9 ± 1.5
	score	2.1 ± 1.0	*0.0011**	2.6 ± 1.0	*< 0.0001**	3.1 ± 0.8
EIA	diameter [mm]	4.3 ± 1.5	*0.0003**	5 ± 1.4	*< 0.0001**	5.8 ± 1.3
	score	1.8 ± 1.0	*0.0096**	2.2 ± 1.1	*0.0007**	2.6 ± 1.0
IIA	diameter [mm]	0.9 ± 1.4	*< 0.0001**	1.3 ± 1.6	*0.0002**	2 ± 1.8
	score	1.5 ± 0.8	*0.0096**	1.8 ± 1.0	*0.1997*	2.0 ± 1.1
PA	diameter [mm]	3.4 ± 1.8	*0.0039**	4 ± 1.5	*0.0064**	4.5 ± 1.1
	score	2.1 ± 1.2	*0.0004**	2.6 ± 1.2	*0.1997*	2.8 ± 1.2
PFA	diameter [mm]	2.8 ± 1.6	*0.0016**	3.4 ± 1.5	*0.0298**	3.7 ± 1.3
	score	1.7 ± 1.0	*0.0138**	2.0 ± 1.1	*0.0138**	2.3 ± 1.1
SFA	diameter [mm]	3.4 ± 1.8	*0.0004**	4.2 ± 1.7	*0.0123**	4.6 ± 1.3
	score	2.0 ± 1.2	*0.0280**	2.2 ± 1.3	*0.0014**	2.7 ± 1.2

cols. The average subjective score was improved from diagnostic (2.0) to good (2.6), when comparing high-pitch to standard-pitch protocols. We regard this as a strong indicator for a usable scanning protocol. The highest image quality scores and vessel diameters were achieved with a combination of high pitch, short delay and high injection pressure. Additionally, all instances of high-pitch scanning, for all combinations of delay and injection pressure, were rated and measured superior to the standard-pitch models. This is consistent with our hypothesis that high-pitch scanning is beneficial to CO_2-CTA. We consider this a sign of correct timing of the CT scan and the CO_2 bolus, with the CT scan beam advancing with the CO_2 bolus. For combinations with a higher injection pressure, the improved values can be at least partially attributed to a higher radial force exhibited by the gas pressure, leading to improved distension of the vessels. To which extent this effect can be translated to a heavily calcified vasculature with reduced compliance remains unclear. To date, dual-source CT is the only technology providing the means for high-pitch CT examinations. Therefore, these results are confined to scanners equipped with this option. It is conceivable, that ongoing developments such as the introduction of wider detectors will allow for similar scan speed as current dual-source technology. CO_2 CT angiography is an invasive procedure in comparison to conventional CTA and MRA [17 – 20], thereby increasing the risk of local complications at the arterial puncture site. As CO_2 has an extremely low viscosity, the use of 4F or even 3F catheter systems appears to be feasible [21]. The risk of complications at the puncture site therefore appears to be acceptable, when weighed against the adverse effects of iodinated or Gd-based contrast media. Especially patients with impaired renal function could benefit from the use of CO_2 for CTA, as has been shown for conventional angiography [22, 23]. In the proposed setting a brachial approach would be recommendable, as a retrograde femoral approach would potentially obstruct the flow of CO_2 into the limb arteries. Instead of performing the arterial puncture in the angiography suite and then transferring the patient to the CT room, the use of a reasonable portable C-arm image intensifier with the patient on the CT table could be used to ensure correct placement of the catheters.

As for diagnostic angiographic CO_2 procedures, subject positioning with elevated placement of the legs is important [7]. This minimizes problems due to the buoyancy of the CO_2 gas, which usually leads to better depiction of non-dependent vessel parts.

Another disadvantage of conventional CO_2 angiography is the need for multiple CO_2 applications for stepwise depiction of the aorto-peripheral arteries. This is time-consuming as a minimum interval of 2 minutes is recommended between repeated injections. It also contributes to patient discomfort, as pain is a commonly reported side effect of CO_2 angiography. In contrast, CO_2-CTA requires only a single insufflation of CO_2, thereby reducing the examination time and minimizing patient distress. With a single gas administration, the pain should be minimal and pain-related motion artifacts, as known from conventional CO_2 DSA, should be minimal. However, dynamic evaluation of the gas propagation will not be possible with CO_2 CTA.

CO_2-CTA is a high-contrast technology with a contrast difference of ca. 1000 Hounsfield units (HU) between the vessel walls and the CO_2 gas. In comparison, typical HU differences of 200 – 400 HU can be expected for examinations using iodinated contrast agents. Thus, low-dose examinations, with a dose even lower than the significant dose reduction achieved in this study, are conceivable for CO_2-CTA, thus justifying the use of CO_2 CT in younger patients, e. g. following a renal transplantation. The principle of dose reduction in CO_2 applications had been shown earlier, although not for CO_2-CTA [8]. Recent developments in CT reconstruction algorithms such as iterative reconstruction could further reduce the needed dose [24].

Limitations

Because healthy animals were used, it is conceivable that the diagnostic yield of CO_2 CT in severely artherosclerotic or elongated and tortuous vessels differs from the findings of this study. This means that the diagnostic accuracy of CO_2 CTA with regards to the detection and quantification of vascular pathology (e. g. stenoses) is still unclear. Moreover, the porcine arterial system is different from that of the human with regard to vessel diameter and length. We did not use conventional CO_2 DSA for comparison, but since this study's aim was to optimize CT and image quality of healthy vessels, we felt that this was not needed to meet the study objectives.

Conclusion

High-pitch, low-delay, high-pressure CT protocols improve carbon dioxide angiography of the lower leg, paving the way for further testing of the method in patients.

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