Thieme

Contrast Media Administration in Coronary Computed Tomography Angiography – A Systematic Review

Einfluss verschiedener Kontrastinjektionsparameter auf das Kontrastenhancement der Koronararterien in der CT-Angiografie – eine Übersichtsarbeit

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ZUSAMMENFASSUNG

Hintergrund Die Kontrastierung der Koronararterien in der CT wird durch verschiedene Parameter der Kontrastmittelinjektion beeinflusst. Bislang existiert in der Literatur kein allgemeingültiger Konsens zu einem optimalen Kontrastmittelinjektionsprotokoll. Das Ziel dieser Übersichtsarbeit war es, die vorhandene wissenschaftliche Literatur systematisch zu analysieren, um den Einfluss der verschiedenen Injektionsparameter zu bestimmen.

Methode Hierzu wurden peer-reviewed Studien analysiert, welche in Pubmed, Embase und MEDLINE zwischen Januar 2001 und Mai 2014 publiziert wurden. Mithilfe bestimmter vorher festgelegter Kriterien wurden in Frage kommende Studien evaluiert. Zu Beginn wurden 2551 mögliche Studien ausgewählt. Nach Analyse der Kriterien wurden letztendlich 36 Studien herausgefiltert, welche systematisch bezüglich ihrer Qualität mittels eines standardisiertem Bewertungsverfahren (Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-II checklist) beurteilt wurden.

Ergebnisse Innerhalb dieser Studien zeigte sich eine sehr heterogene und teils inkomplette Datenlage, was eine exakte Vergleichbarkeit sehr schwierig macht. Es bleibt weiterhin nicht in letzter Konsequenz zu beantworten, welcher Parameter entscheidend für eine optimale Kontrastierung der Koronararterien ist. Wahrscheinlich ist daher ein Parameter wie die Jodapplikationsrate (Iodine Delivery Rate) optimal, da dieser mehrere Faktoren (Kontrastkonzentration und Flussrate) miteinander verbindet.

Schlussfolgerung Da zukünftige Kontrastforschung sich auf eine verstärkt individualisierte Kontrastgabe richtet, sollten weitere (möglichst große randomisierte) Studien durchgeführt werden, welche die offenen Fragen bezüglich des Einflusses der einzelnen Parameter beantworten können.

Kernaussagen:
- Die vorliegende Arbeit gibt eine systematische Übersicht der entscheidenden Einflussfaktoren auf die optimale Kontrastierung der Koronarien.
- Verschiedene teils widersprüchliche Resultate wurden bislang in der Literatur bezüglich der Kontrastierung der Koronarien beschrieben.
- Die Jodapplikationsrate ist wahrscheinlich entscheidend, da dieser Parameter die zwei wichtigsten Faktoren miteinander kombiniert.
- Weitere Forschung ist notwendig, um die Jodapplikationsrate für den individuellen Patienten zu optimieren.
- Weitere Forschung ist notwendig, um den genauen Einfluss von verschiedenen Einzelfaktoren zu untersuchen.

ABSTRACT

Background Various different injection parameters influence enhancement of the coronary arteries. There is no consensus in the literature regarding the optimal contrast media (CM) injection protocol. The aim of this study is to provide an update on the effect of different CM injection parameters on the coronary attenuation in coronary computed tomographic angiography (CCTA).

Method Studies published between January 2001 and May 2014 identified by Pubmed, Embase and MEDLINE were evaluated. Using predefined inclusion criteria and a data extraction form, the content of each eligible study was assessed. Initially, 2551 potential studies were identified. After applying our criteria, 36 studies were found to be eligible. Studies were systematically assessed for quality based on the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-II checklist.

Results Extracted data proved to be heterogeneous and often incomplete. The injection protocol and outcome of the included publications were very diverse and results are difficult to compare. Based on the

extracted data, it remains unclear which of the injection parameters is the most important determinant for adequate attenuation. It is likely that one parameter which combines multiple parameters (e. g. IDR) will be the most suitable determinant of coronary attenuation in CCTA protocols.

Conclusion Research should be directed towards determining the influence of different injection parameters and defining individualized optimal IDRs tailored to patient-related factors (ideally in large randomized trials).

Key points

- This systematic review provides insight into decisive factors on coronary attenuation.
- Different and contradicting outcomes are reported on coronary attenuation in CCTA.
- One parameter combining multiple parameters (IDR) is likely decisive in coronary attenuation.
- Research should aim at defining individualized optimal IDRs tailored to individual factors.
- Future directions should be tailored towards the influence of different injection parameters.

Citation Format

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Introduction

Technical advances in coronary computed tomographic angiography (CCTA) continuously improved image quality [1]. Current technologies enable single-heartbeat CCTA with wide-area detectors [2], dual source technique or high pitch acquisition [3]. This leads to a substantial reduction in scan acquisition time (< 1 – 6 s, depending on scan protocol) as well as a decrease in motion artifacts due to breathing and coronary motion [4]. As these technical advances facilitate shorter scan acquisition times, smaller volumes of contrast media (CM) may be used (total iodine dose [TID]) [5, 6].

Previous studies demonstrated that enhancement levels in the coronary arteries above 325 Hounsfield units (HU) are necessary for optimal diagnosis [7 – 9]. Arterial attenuation depends on injection-related parameters (e. g. iodine delivery rate [IDR; gI/s], injection rate [ml/s], CM concentration [mg/ml], TID, CM volume, viscosity, saline flush, temperature of injected CM and injection needle type), scan-related parameters (e. g. scan protocol, scan duration, scan delay, tube voltage, and reconstruction parameters [kernel]) and patient-related factors (e. g. cardiac output, blood volume, heart rate, breath hold and weight) [1, 10, 11]. The influence of these individual parameters is important as future directions are aimed towards more individualized CM injection protocols. Previous research has focused on the influence of saline flush, IDR, injection rate, CM concentration, injection needle size, CM volume, viscosity as well as the temperature of injected CM on intravascular attenuation with various outcomes [1, 10 – 20]. Specifically, the influence of CM concentration has been studied extensively, and current evidence is controversial as to whether a more highly concentrated CM is beneficial in intravascular attenuation, when the calculated IDR (e. g. CM concentration × injection rate) is kept identical [12, 15, 16, 18 – 20]. To date, there is no consensus regarding the decisive injection parameters influencing attenuation of the coronary arteries.

A systematic review of the literature on current CM application protocols for CCTA was performed with the aim of providing an overview of the influence of various injection factors on enhancement of the coronary arteries with a special focus on IDR, CM concentration and injection rate.

Methods

Data sources and study selection

For this systematic review, we conducted a search through PubMed, Embase and MEDLINE between January 2001 and May 2014 using the search terms coronary computed tomography angiography, coronary computed tomography, iodine delivery rate, coronary attenuation, coronary enhancement, total iodine load, coronary arteries, iodine concentration, contrast media concentration, contrast material concentration.

Inclusion criteria were: (1) studies had to compare different CM injection protocols in CCTA by providing attenuation levels in the coronaries achieved by a specific infusion protocol, (2) an evaluation of image quality and/or diagnostic accuracy was reported, (3) sample size of ≥ 30 (> 18 years old), (4) language English, German or French, (5) MDCT ≥ 16 slice and (6) IDR, injection rate, CM concentration, TID, CM volume had to be deduced. Studies conducted primarily on radiation dosage, other technical aspects (e. g. reconstruction kernels, bolus tracking technique/test bolus method), central venous or intra-arterial CM delivery, or focusing on patients with stents or bypasses were excluded. Three readers (CM, JT, AS) independently performed the searches and assessed the eligibility of the studies by reading the abstract and application of these criteria. All potentially eligible articles were screened for references to additional eligible studies. Disagreement on inclusion was solved by consensus between the three readers.

Data extraction

Publications considered eligible were scored using a standardized extraction form, for the following variables: design (retrospective/prospective/both), population region/size, age, weight/body mass index (BMI), height, heart rate, cardiac output, blood pressure, MDCT technique, slice collimation, rotation time, acquisition mode, kV settings, reconstructed slice thickness, reconstruction kernel, intravenous (i. v.) needle size, CM concentration, CM volume, injection rate, injection duration, saline flush, injection pattern, temperature, IDR, TID and enhancement level at different coronary arteries.

In addition, the quality of the studies regarding selection and inclusion criteria, study aims, patient characteristics and methodology was assessed and a flowchart was created according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines [21]. Studies were also systematically

assessed for quality based on the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-II checklist [22]. This checklist assesses the risk of bias and clinical applicability of studies based on different domains. Some of the domains are not applicable to the included studies, as this review does not focus on strict diagnostic studies. Therefore, only domains relevant to our study were selected from QUADAS-II for quality assessment. Results from the QUADAS-II assessment are depicted in a graphical manner.

Additionally, the corresponding authors of all included studies were contacted to fill out a questionnaire providing additional parameters that could not be retrieved from the publication. The large heterogeneity observed between the included studies regarding patient population, scanning technique and infusion parameters precluded us from pooling the data and only allowed a systematic review. To account for heterogeneity with regard to the outcome measure, a subgroup analysis of the most frequently studied anatomical location (RCA) was performed (e. g. 30 studies) to evaluate the influence of injection-related parameters on coronary attenuation. Since this study is a systematic literature review, no approval from our institutional review board was necessary.

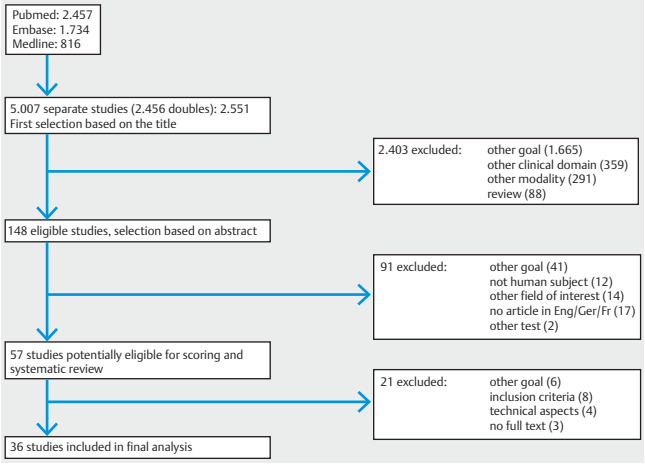
Results

In the primary literature search, 5007 potential studies (Pubmed: 2457, Embase: 1734, Medline: 816) were identified, of which 2456 were duplicates, leaving 2551 potential studies for analysis. 2403 studies were excluded from further evaluation after scanning of the abstract. Of the remaining 148 studies, 91 studies did not meet the eligibility criteria and were further excluded, leaving 57 studies to be reviewed using the extraction form and consensus reading. Another 21 studies were excluded as they addressed other technical aspects or because basic inclusion criteria and/or injection parameters could not be derived [23 – 43]. In total, 36 studies were included with a total of 4339 patients [7, 15, 16, 19, 44 – 75]. Of the included studies, 18 authors responded to the questionnaire [7, 19, 49, 51, 54 – 57, 60, 61, 63 – 67, 70, 72, 75. A detailed overview of the inclusion and data extraction process is depicted in ▶ **Fig. 1**.

Data was prospectively collected in the vast majority (81 %) of the included studies. According to the QUADAS-II assessment, there were some concerns regarding the risk of bias and applicability mainly in the domain regarding patient selection. For the other domains a low risk of bias was found. Results of the QUADAS-II assessment are shown in ▶ **Fig. 2**. The quality assessment of all included publications is presented in the supplemental material.

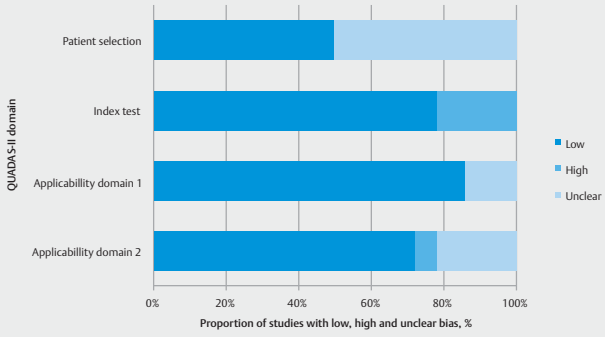
Scan and patient-related parameters are described in ▶ **Table 1, 2**. Baseline characteristics were poorly described, only reporting mean age, heart rate and weight. Approximately 20 publications state one or more additional baseline characteristics (e. g. BMI, cardiac output or blood pressure) [7, 48, 52, 54 – 57, 63 – 75]. In the vast majority of the included publications, a tube voltage of 120 kV was used. Some of the included papers either did not mention tube voltage or mention lower or various kV settings [48, 59, 63, 70, 73, 74]. As different vendors and scanners were used, scan-related parameters such as collimation, slice reconstruction and kernel were not comparable and occasionally missing.

Injection-related parameters are described in ▶ **Table 3**. The temperature of the injected CM concentration was only stated in a limited number of publications [15, 19, 52, 56, 58, 60 – 62, 65 – 67, 72]. A saline flush was initially not used in all injection protocols but has gained increasing popularity in more recent publications with only a few publications using injection protocols without a saline flush [44 – 46, 49, 57, 58, 72]. Only eight publications state usage of a biphasic protocol, often in comparison to a uniphasic injection protocol [45 – 47, 49, 53 – 55, 57]. The total injected CM volume ranged between 30 ml and 140 ml. Within the period of inclusion, a gradual decrease in total injected CM volume is noted, as earlier publications make mention of a total injected CM volume of 140 ml [15, 44, 45], whereas more recent publications reported CM injection protocols with total injected CM volumes below 40 ml [69, 70, 74, 75]. Subsequently, the TID has substantially lowered from anywhere between 44 – 56 g [15, 44, 45] to less than 15 g (range: 11.1 – 56.0 g) [7, 47, 60, 61, 64, 68 – 71].



▶ **Fig. 1** Detailed overview study selection.

▶ **Abb. 1** Detail Übersicht zu den ausgewählten Studien.



▶ **Fig. 2** Graphical display of different domains of the QUADAS II checklist for all included studies (n = 36).

▶ **Abb. 2** Grafische Darstellung der QUADAS-II-Domänen der eingeschlossenen Studien (n = 36).

▶ **Table 1** Scan characteristics of the included studies listed according to year of publication.

▶ **Tab. 1** Scan-Parameter der eingeschlossenen Studien. Reihenfolge nach Jahr der Publikation.

author	coll (mm)	rot time (ms)	acquisition mode	kV setting	slice reconstr (mm)	kernel
Cademartiri [44]	12x× 0.75	420	ECG gating	120	1	medium smooth (B30f)
Cademartiri [15]	16 × 0.75	420	ECG gating	120	1	medium smooth (B30f)
Cademartiri [45]	16 × 0.75	420	ECG gating	120	1	
Cademartiri [16]	16 × 0.75	375	ECG gating	120	1	medium smooth (B30f)
Rist [19]	16 × 0.75	375	ECG gating	120	1	B20f
Utsunomiya [46]	16 × 0.5	400	ECG gating	120		
Yamamuro [47]	64 × 0.5	400		120	0.5	
Husmann [48]	64 × 0.625	350	ECG triggering			
Kerl [49]	2 × 32 × 0.6	330	ECG gating	120	0.75	medium smooth (B25f)
Kim [50]	64 × 0.6	370	ECG gating	120		medium smooth (B25f)
Nakaura [51]	64 × 0.625	420	ECG gating	120	0.67	medium cardiac
Tsai [52]	40 × 0.625	420	ECG gating	120	1.4 – 3	
Wuest [53]	64 × 0.6	330	ECG gating	120	0.75	medium sharp (B26f)
Halpern [54]	64 × 0.9	420	ECG gating/triggering	120	0.8	cardiac sharp C
Seifarth [55]	2 × 32 × 0.6	330		120		
Kim [56]	64 × 0.5	400	ECG gating	120	0.5	FC43
Lu [57]	64 × 0.625	350	ECG gating	120		
Ozbulbul [58]	16 × 0.625	500	ECG gating	120	0.625	medium soft tissue
Pazhenkottil [59]	64 × 0.625	350	ECG triggering	100 – 120	0.625	
Tatsugami [60]	320 × 0.5	350/375	ECG gating	120	0.5	FC13
Tatsugami [61]	64 × 0.5	350/400	ECG triggering	135	0.5	FC13
Becker [62]		330	ECG gating	120	0.6	B26
Isogai [7]	64 × 0.625	350	ECG gating	120	0.625	cardiac
Kumamaru [63]	320 × 0.5	350	ECG triggering	80/100/120		FC03
Nakaura [64]	64 × 0.625	420	ECG gating	120	0.67	medium cardiac (XCB)
Zhu [65]	2 × 64 × 0.6	330	ECG gating	120	0.75	medium soft tissue (B26f)
Zhu [66]	2 × 64 × 0.6	330	ECG gating	120	0.75	medium soft tissue (B26f)
Zhu [67]	2 × 64 × 0.6	330	ECG gating	120	0.75	medium soft tissue (B26f)
Kidoh [68]	64 × 0.625	420	ECG gating	120	0.67	medium cardiac (XCB)
Kidoh [69]	64 × 0.625	420	ECG gating	120	0.67	medium cardiac (XCB)
Liu [70]	2 × 128 × 0.6	280	ECG triggering	100	0.75	medium smooth (B26)
Yang [71]	2 × 128 × 0.6	280	ECG triggering	120	0.6	media smooth (B26f)
Tomizawa [72]	320 × 0.5	350/375/400	ECG triggering	120	0.5	FC04, AIDR
Zheng [73	2 × 64 × 0.6	280	ECG triggering	80/100 100/120	0.75	I26F B26f
Lembcke [74]	2 × 128 × 0.6	280	ECG triggering	100		
Kawaguchi [75]	2 × 128 × 0.625	270	ECG gating	120	0.8	medium cardiac (XCB)

Coll: collimation, rot: rotation, reconstr: reconstruction, BMI: body mass index.
Coll: Kollimation, Rot: Rotation, Reconstr.: Rekonstruktion, BMI: Body Maß Index.

▶ **Table 2** Patient characteristics of the included studies listed according to year of publication.

▶ **Tab. 2** Patienten Charakteristika der eingeschlossenen Studien. Reihenfolge nach Jahr der Publikation.

author	no. of subjects (m;f)	mean age (years)	mean weight (kg)	BMI (kg/m²)	heart rate (bpm)	CO (l/min)/ EF (%)	BP (syst; diast, mmHg)
Cademartiri [44]	21 (16;5)	59 (34 – 74)	72 (53 – 90)		60 (48 – 72)		
	21 (14;7)	59 (39 – 79)	74 (60 – 95)		60 (49 – 80)		
Cademartiri [15]	25 (22;3)	58 ± 11	74 ± 7		59 ± 8		
	25 (20;5)	60 ± 11	72 ± 7		59 ± 7		
	25 (21;4)	58 ± 13	72 ± 7		61 ± 9		
	25 (21;4)	57 ± 11	74 ± 9		60 ± 9		
	25 (20;5)	63 ± 12	71 ± 8		57 ± 8		
Cademartiri [45]	15 (11;4)	58 (34 – 74)	71 (55 – 90)		58 (46 – 72)		
	15 (14;1)	58 (28 – 73)	72 (60 – 88)		56 (45 – 65)		
	15 (14;1)	59 (45 – 79)	73 (60 – 95)		56 (45 – 68)		
Cademartiri [16]	20 (15;5)	59 ± 12	73 ± 9		61 ± 7		
	20 (14;6)	63 ± 10	75 ± 11		60 ± 8		
Rist [19]	30	58.13 ± 11.16	77.68 ± 14.76		57.3 ± 3.7		
	30	62.17 ± 8.22	84.86 ± 16.24		57.4 ± 4.3		
Utsunomiya [46]	13 (total: 30;8)	68.6 ± 8.4	59.5 ± 7.0		61 ± 11		
	12	63.9 ± 8.9	62.1 ± 8.5		59 ± 11		
	13	68.0 ± 8.8	64.3 ± 7.1		58 ± 8		
Yamamuro [47]	30 (16;14)	68.7 ± 12.1	59.5 ± 11.7		70.1 ± 13.1		
	30 (17;13)	68.0 ± 11.0	57.3 ± 7.8		72.7 ± 18		
Husmann [48]	70 (48;22)	58 ± 12	79 ± 16	26.5 ± 4.0	57.7 ± 7.0		
	70 (51;19)	60 ± 11	80 ± 15	26.7 ± 4.2	57.6 ± 6.0		
Kerl [49]	25 (14;11)	53.32	82.2				
	25 (20;5)	65.40	87.7				
	25 (14;11)	65.84	86.9				
Kim [50]	20 (total: 59;41)	62 (44 – 82)	62 (54 – 78)		55 (42 – 67)		
	20	56 (43 – 76)	67 (53 – 79)		58 (47 – 74)		
	20	57 (37 – 76)	61 (51 – 75)		59 (43 – 79)		
	20	58 (39 – 77)	64 (53 – 79)		58 (41 – 71)		
	20	57 (38 – 72)	66 (52 – 83)		61 (51 – 74)		
Nakaura [51]	30 (13;17)	62.4 ± 12.5	60.1 ± 14.2		66.5 ± 12.5		
	30 (16;14)	67.5 ± 12.9	59.5 ± 12.8		65.8 ± 12.9		
Tsai [52]	38 (22;16)	61.7 ± 12.5	64.9 ± 10.9		71.5 ± 13.2	58.8 ± 6.5	120.7 ± 14.5; 75.4 ± 10.5
	34 (21;13)	61.7 ± 11.3	65.9 ± 8.4		76.7 ± 11.2	57.0 ± 5.6	118.9 ± 12.6; 75.8 ± 9.0
Wuest [53]	53 (38;15)	58 ± 11.82					
	53 (40;13)	62 ± 13.08					
Halpern [54]	260 (%: 57;43)	58 ± 12	89 ± 25	30.3 ± 7.6	61.5 ± 0.8		Syst> 100
	168 (%: 45;55)	50 ± 12	85 ± 21	29.6 ± 6.7	63.0 ± 1.0		
Seifarth [55]	40	62.3 ± 10.8	80.8 ± 14.2	26.3 ± 3.0	64.7 ± 13.0		
	40	62.6 ± 9.6	82.0 ± 13.4	26.2 ± 3.7	63.1 ± 11.4		
	40	62.9 ± 13.3	81.7 ± 15.3	26.3 ± 3.8	63.7 ± 13.3		

▶ **Table 2** (Continuation)

author	no. of subjects (m;f)	mean age (years)	mean weight (kg)	BMI (kg/m²)	heart rate (bpm)	CO (l/min)/ EF (%)	BP (syst; diast, mmHg)
Kim [56]	151 (87;64)	55 ± 9	67 ± 10.2	24.6 ± 3.0	70 ± 11		124 ± 18 (85 – 169)
	146 (88;58)	52 ± 11	68 ± 9.9	24.8 ± 2.7	71 ± 11		128 ± 19 (92 – 181)
Lu [57]	30 (total: 71;79)	55.6 ± 10.9		23.4 ± 2.4	58.0 ± 8.0		
	30	58.8 ± 12.2		23.8 ± 2.6	58.4 ± 6.3		
	30	58.8 ± 10.5		23.7 ± 2.5	57.9 ± 7.5		
	30	58.3 ± 11.5		23.5 ± 2.3	57.6 ± 6.7		
	30	56.1 ± 11.2		24.3 ± 2.5	56.1 ± 6.8		
Ozbulbul [58]	24 (total: 20;32)	56.4 ± 13.6			61.0 ± 8.9		
	28	54.1 ± 17.1			62.8 ± 7.0		
Pazhenkottil [59]	80 (59;21)	59 ± 11	82 ± 12		56 ± 7		
	80 (68;12)	57 ± 11	82 ± 12		56 ± 7		
Tatsugami [60]	48 (57;41)	69.8 ± 9.8	59.3 ± 8.4		57.1 ± 9.7		
	50	68.7 ± 9.0	58.0 ± 8.1		58.8 ± 6.4		
Tatsugami [61]	16 (total: 27;18)	68.2 ± 10.6	57.4 ± 6.0		53.8 ± 7.6		
	15	69.1 ± 10.3	55.3 ± 5.9		55.7 ± 7.7		
	14	69.6 ± 9.6	56.2 ± 7.8		59.0 ± 12.2		
Becker [62]	50 (28)	57.0 ± 11.2	77.4 ± 17.7		66.5 ± 14.26		
	54 (31)	60.4 ± 11.6	78.0 ± 19.1		68.1 ± 15.86		
Isogai [7]	20 (16;4)	63.5 ± 11.4	63.9 ± 13.7		62.1 ± 10.9		133.8 ± 14.3; 79.9 ± 8.8
	20 (12;8)	64.4 ± 11.7	64.4 ± 13.3		63.0 ± 8.2		133.± 17.9; 82.0 ± 11.8
	20 (5;15)	65.4 ± 7.8	66.0 ± 8.5		62.9 ± 10.5		138.3 ± 16.9; 80.6 ± 12.7
Kumamaru [63]	36 (18;18)	56.7 ± 12.9	79.7 ± 15.4	22.8 ± 4.8	57.4 ± 5.9		
	72 (41;31)	54.8 ± 11.9	80.8 ± 18.0	27.8 ± 4.8	56.7 ± 5.9		
Nakaura [64]	30 (21;9)	69.9 ± 9.1	56.8 ± 9.2	22.4 ± 3.1	60.0 ± 9.7	4.2 ± 0.9	
	30 (20;10)	70.9 ± 11.6	57 ± 10	22.9 ± 3	59.8 ± 10.9	4.2 ± 1.0	
Zhu [65]	96 (57;39)	58.2 (29 – 85)	67.1 (39 – 101)	24.5 (15.8 – 34)	71.7 (48 – 106)	6.2 ± 1.7	
	100 (53;47)	58.1 (27 – 84)	67.9 (40 – 101)	24.6 (17.9 – 35.4)	74.5 (51 – 107)		
	100 (53;47)	59.8 (30 – 83)	65.9 (41 – 104)	24.1 (15.2 – 34.9)	73.0 (50 – 104)		
Zhu [66]	114 (60;54)	60.8 (30 – 85)	66.9 (34 – 100)	24.7 (16.4 – 32.7)	74.5 (49 – 107)		
	119 (67;52)	59.8 (28 – 83)	67.1 (38 – 94)	24.7 (16.9 – 32.0)	75.7 (50 – 111)		
Zhu [67]	113 (60;53)	58.2 (30 – 85)	66.9 (34 – 100)	24.7 (16.4 – 32.7)	74.5 (49 – 107)		
	94 (54;40)	60.4 (32 – 87)	64.8 (42 – 101)	23.9 (16.4 – 33.0)	74.3 (37 – 106)		
Kidoh [68]	50 (32;18)	70.7 ± 9.5	57.2 ± 10.4	22.6 ± 3.2	60.1 ± 10.3	4.2 ± 1.5	
	50 (32;18)	68.5 ± 11.4	56.8 ± 10.2	22.3 ± 2.9	60.6 ± 11.8	4.1 ± 1.2	
Kidoh [69]	30 (18;12)	68.1 ± 12	57.7 ± 13.3		64.1 ± 11.0	4.6 ± 1.3	
	30 (21;9)	59.9 ± 14.3	61.6 ± 10.0		62.8 ± 11.4	4.6 ± 1.2	
Liu [70]	30 (total: 60;30)	55 ± 13	71 ± 12	25.0 ± 2.8	56 ± 6	> 55 %	150;80
	30	59 ± 10	71 ± 9	24.9 ± 2.4	58 ± 5		
	30	52 ± 11	73 ± 13	25.3 ± 3.2	57 ± 5		

▶ **Table 2** (Continuation)

author	no. of subjects (m;f)	mean age (years)	mean weight (kg)	BMI (kg/m²)	heart rate (bpm)	CO (l/min)/ EF (%)	BP (syst; diast, mmHg)
Yang [71]	120 (81;39)	58.5 ± 9.8	68.7 ± 11.1	24.1 ± 3.0	59.1 ± 7.5		
	80 (53;27)	59.6 ± 9.7	69.0 ± 10.1	23.7 ± 2.8	59.3 ± 6.8		
Tomizawa [72]	36 (20;16)	66.1 ± 14.4	59.3 ± 12.1	23 ± 3.6	67.5 ± 11.5		
	36 (16;20)	67.9 ± 12.6	55.9 ± 8.8	22.3 ± 3.0	65.8 ± 13.6		
	36 (17;19)	67.1 ± 9.8	61.3 ± 13.7	23.7 ± 3.2	57.4 ± 11.2		
Zheng [73]	50 (25;25)	54.53 ± 10.71	65.45 ± 11.13	22.31 ± 2.77	75.61 ± 9.59		
	25 (12;13)	BMI< 25: 56.39 ± 12.79	BMI< 25: 57.57 ± 6.65	BMI< 25: 20.9 ± 1.49	BMI< 25: 75.35 ± 10.13		
	25(13;12)	BMI≥ 25: 52.88 ± 8.39	BMI≥ 25: 72.42 ± 9.56	BMI≥ 25: 25.44 ± 1.63	BMI≥ 25: 75.85 ± 9.29		
	50 (31;19)	55.24 ± 9.38	64.55 ± 12.91	23.73 ± 3.39	72.67 ± 9.89		
	25 (12;13)	BMI< 25: 58.56 ± 9.43	BMI< 25: 54.28 ± 6.36	BMI< 25: 20.79 ± 1.32	BMI< 25: 72.76 ± 10.49		
	25 (19;6)	BMI≥ 25: 52.04 ± 8.30	BMI≥ 25: 74.42 ± 9.35	BMI≥ 25: 26.56 ± 2.09	BMI≥ 25: 72.58 ± 9.49		
Lembcke [74]	20 (8;12)	75.7 ± 7.4	76 ± 7.8	25.9 ± 2.9			
	20 (13;7)		76.1 ± 8.1	25.2 ± 2.2			
	20 (8;12)		76.6 ± 6.6	26.4 ± 2.6			
	20 (9;11)		74.5 ± 7.1	25.9 ± 2.1			
	20 (10;10)		75.9 ± 8.0	26.2 ± 2.5			
Kawaguchi [75]	50 (32;18)	63.3 ± 12	64.7 ± 11.1	24.6 ± 3.5	66.1 ± 11.7		
	50 (27;23)	65.3 ± 11.5	62.5 ± 12.7	24.1 ± 3.8	63.7 ± 7.2		

M: male, F: female, kg: kilograms, BMI: body mass index, BPM: beats per minute, CO: cardiac output, EF: ejection fraction, BP: blood pressure, syst: systolic, diast: diastolic.
M: männlich, F: weiblich, kg: Kilogramm, BMI: Body Maß Index, BPM: Beats pro Minute, CO: Kardialer Output, EF: Ejektion Fraktion, BP: Blutdruck, Syst.: Systole, Dias: Diastole.

Injection-related parameters and coronary attenuation

The results of all included publications in relation to its three major injection parameters are presented in the supplemental material. The CM concentration varied between 270 mg/ml and 400 mg/ml. However, only four CM injection protocols make use of CM concentrations below 320 mg/ml [7, 15, 19, 73]. The variation in injection rate was higher than for CM concentrations, varying between 2.5 ml/s [19] and 6 ml/s [55, 63, 70]. The majority of the included papers keep injection rate relatively constant when comparing different groups. Only a few studies mention substantial differences in flow rates between groups [19, 55, 61, 75]. IDR ranged between 0.99gI/s and 2.22gI/s and proved to be very heterogeneous. A limited number of injection protocols stated usage of an IDR above 1.9gI/s [54, 55, 63, 70]. All included publications that stated a flow rate below 4 ml/s also reported an IDR < 1.4gI/s [7, 46, 47, 61, 64, 75]. However, lower CM concentrations were not always associated with lower IDR levels, as some publications state IDR levels ≥ 1.4gI/s with usage of lower (e. g. 320 mg/ml) CM concentrations, indicating that the CM injection rate might have a greater influence on the calculated IDR [45, 48, 59].

Conflicting results were reported with regard to the influence of IDR on coronary attenuation. When the IDR differed between subgroups, various publications found significant differences in the attenuation of the coronary arteries in favor of a higher IDR [7, 15, 16, 55, 61, 62, 68, 69, 75]. When the IDR between subgroups was kept identical, numerous publications did not find statistically significant differences in coronary attenuation [7, 15, 19, 44 – 46, 49, 51, 60, 70, 71]. In both groups (variable and identical IDR), other injection-related parameters varied substantially, making it difficult to determine the true influence of IDR on coronary attenuation [47, 50, 53, 55, 57, 63, 74]. Three studies report significant differences between CM concentrations in favor of higher CM concentrations [15, 16, 62]. However, other injection parameters such as IDR were not kept identical between groups.

Diagnostic attenuation levels of the RCA were reached in the vast majority of the included studies when IDR levels ≥ 1.4gI/s were used. Only seven studies report non-diagnostic attenuation

▶ **Table 3** Injection parameters of the included studies listed according to year of publication.

▶ **Tab. 3** Kontrastinjektionsparameter der eingeschlossenen Studien. Reihenfolge nach Jahr der Publikation.

author	needle	CM (mg/ml)	CM volume (ml)	flow rate (ml/s)	saline	injection pattern	temp (°C)	IDR (gI/s)	TID (g)
Cademartiri [44]	18G	iodixanol 320	140	4	no	uniphasic		1.28	44.8
		iodixanol 320	100	4	yes	uniphasic		1.28	32
Cademartiri [15]	18G	iohexol 300	140	4	no	uniphasic		1.2	42
		iodixanol 320	140	4	no	uniphasic	37	1.28	44.8
		iohexol 350	140	4	no	uniphasic	37	1.4	49
		iomeprol 350	140	4	no	uniphasic	37	1.4	49
		iomeprol 400	140	4	no	uniphasic	37	1.6	56
Cademartiri [45]	18 – 20G	iodixanol 320	140	4	no	uniphasic		1.28	44.8
		iodixanol 320	140	5→3	no	biphasic		1.6→0.96	44.8
		iodixanol 320	100	4	no	uniphasic		1.28	32
Cademartiri [16]	18G	iopromide 370	100	4	yes	uniphasic		1.48	37
		iomeprol 400	100	4	yes	uniphasic		1.6	40
Rist [19]	18G	iomeron 300	83	3.3	yes	uniphasic	37	0.99	24.9
		iomeron 400	63	2.5	yes	uniphasic	37	1.0	25.2
Utsunomiya [46]	20G	iohexol 350	60 + mix 80 (50 %)	3→1.5	no	biphasic		1.05→0.26	35
		iohexol 350	100	3	yes	uniphasic		1.05	35
		iohexol 350	100	3	no	uniphasic		1.05	35
Yamamuro [47]		iomeron 350	40	3.5→2.8	yes	biphasic		1.23→0.9-8	14
		iomeron 350	50	3.5→2.8	yes	biphasic		1.23→0.9-8	17.5
Husmann [48]	18G	iodixanol 320	80	5	yes	uniphasic		1.6	25.6
		iodixanol 320	73.9 ± 11.2	4.0 – 5.0	yes	uniphasic		1.28 – 1.6	23.6
Kerl [49]	18G	iopamidol 370	50 – 75	5	no	uniphasic		1.85	18.5 – 27.8
		iopamidol 370	50 – 75	5	yes	uniphasic		1.85	18.5 – 27.8
		iopamidol 370	(50 – 75) + mix 50 (30 %)	5	yes	biphasic		1.85→0.5-6	18.5 – 27.8 + 5.6
Kim [50]		iobitridol 350	60	4	yes	uniphasic		1.4	21
		iobitridol 350	60	4	yes	uniphasic		1.4	21
		iobitridol 350	60	4	yes	uniphasic		1.4	21
		iobitridol 350	60	4	yes	uniphasic		1.4	21
		iobitridol 350	60	4	yes	uniphasic		1.4	21
Nakaura [51]	20G	iopamiron 370	80	4	yes	uniphasic		1.48	29.6
		iopamiron 370	59.5 ± 12.8	3.96 ± 0.85	yes	uniphasic		1.47	22.0 ± 4.7
Tsai [52]	20G	iohexol 350	100	4	yes	uniphasic	37	1.4	35
		iodixanol 320	100	4	yes	uniphasic	37	1.28	32
Wuest [53]		iomerol 350	45 – 65	5	yes	uniphasic		1.75	15.75 – 22.75
		iomerol 350	55 – 75 (incl mix 20 %)	5	yes	biphasic		1.75→0.3-5	22.75 – 29.75

▶ **Table 3** (Continuation)

author	needle	CM (mg/ml)	CM volume (ml)	flow rate (ml/s)	saline	injection pattern	temp (°C)	IDR (gI/s)	TID (g)
Halpern [54]	18 – 20G	ioversol 350	70	5.5	yes	uniphasic		1.93	24.5
		ioversol 350	70 + mix 50 (50 %)	5	yes	biphasic		1.75→0.8-8	33.25
Seifarth [55]	18G	iopromide 370	80 + mix 50 (30 %)	6	yes	biphasic		2.22→0.6-7	35.2
		iopromide 370	82.5 ± 8.8 + mix 34.3 ± 10.8(30 %)	5.1 ± 0.6	yes	biphasic		1.89→0.5-7	35.6
		iopromide 370	73.5 ± 12.9 + mix 50 (30 %)	5	yes	biphasic		1.85→0.5-6	32.8
Kim [56]	18G	iomeprol 370	70	4	yes	uniphasic	37	1.48	25.9
		iomeprol 400	70	4	yes	uniphasic	37	1.6	28
Lu [57]	20G	iohexol 350	67 ± 5.3	5	no	uniphasic		1.75	23.45
		iohexol 350	59.9 ± 4.9	5	yes	uniphasic		1.75	20.97
		iohexol 350	(56.9 ± 3.2) + mix 20 (30 %)	5	yes	biphasic		1.75→0.5-3	22.02
		iohexol 350	(59.2 ± 5.7) + mix 20 (50 %)	5	yes	biphasic		1.75→0.8-8	24.22
		iohexol 350	(56.9 ± 4.6) + mix 20 (70 %)	5	yes	biphasic		1.75→1.2-3	24.82
Ozbulbul [58]	18G	iodixanol 320	130	4	no	uniphasic	37	1.28	41.6
		iopamidol 370	130	4	no	uniphasic	37	1.48	48.1
Pazhenkottil [59]	18G	iodixanol 320	80	5	yes	uniphasic		1.6	25.6
		iodixanol 320	70.9 ± 14.1	3.5 – 5.0	yes	uniphasic		1.1 – 1.6	22.7
Tatsugami [60]	20G	iomeron 350	47.5 ± 7.4	4 ± 0.56	yes	uniphasic	37	1.4	16.6
		iomeron 350	41.5 ± 5.5	4.06 ± 0.57	yes	uniphasic	37	1.42	14.5
Tatsugami [61]	20G	iomeron 350	46.5 ± 5.25	3.3 ± 0.37	yes	uniphasic	37	1.16	16.28
		iomeron 350	44.3 ± 4.71	4.4 ± 0.48	yes	uniphasic	37	1.54	15.5
		iomeron 350	39.3 ± 5.41	4.0 ± 0.55	yes	uniphasic	37	1.40	13.76
Becker [62]	18G	iodixanol 320	80	5	yes	uniphasic	37	1.6	25.6
		iomeprol 400	80	5	yes	uniphasic	37	2	32
Isogai [7]	18G	iohexol 300	44.7	4.5	yes	uniphasic		1.35	13.42
		iohexol 350	38.6	3.9	yes	uniphasic		1.37	13.52
		iohexol 350	46.2	4.6	yes	uniphasic		1.61	16.17
Kumamaru [63]	20G	iopamidol 370	60	6	yes	uniphasic		2.22	22.2
		iopamidol 370	80	6	yes	uniphasic		2.22	29.6
Nakaura [64]	20G	iohexol 350	57 ± 10.1	3.8 ± 0.7	yes	uniphasic		1.33 ± 0.23	20
		iohexol 350	39.7 ± 6.4	4.4 ± 0.7	yes	uniphasic		1.55 ± 0.25	13.9
Zhu [65]	20G	iopromide 370	66.3 (42 – 92)	4.15 (2.6 – 5.7)	yes	uniphasic	37	1.54	24.5
		iopromide 370	66.4 (40 – 92)	4.19 (2.6 – 6)	yes	uniphasic	37	1.55	24.6
		iopromide 370	66.4 (37 – 95)	4.08 (2.7 – 5.9)	yes	uniphasic	37	1.51	24.6

▶ **Table 3** (Continuation)

author	needle	CM (mg/ml)	CM volume (ml)	flow rate (ml/s)	saline	injection pattern	temp (°C)	IDR (gI/s)	TID (g)
Zhu [66]	20G	iopromide 370	73.6 ± 13.5	4.69 ± 0.95	yes	uniphasic	37	1.74	27.23
		iopromide 370	67.9 ± 8.3	4.38 ± 0.66	yes	uniphasic	37	1.62	25.12
Zhu [67]	20G	iopromide 370	73.6 (37 – 110)	4.69 (2.3 – 7.4)	yes	uniphasic	37	1.74	27.2
		iopromide 370	68.5 (42 – 111)	4.37 (2.5 – 6.6)	yes	uniphasic	37	1.62	25.3
Kidoh [68]	20G	iohexol 350	40.6 ± 7.6	4.5 ± 0.9	yes	uniphasic		1.58	14.21
		iohexol 350	39.7 ± 7.1	5	yes	uniphasic		1.75	13.90
Kidoh [69]	20G	iohexol 350	36.9 ± 9.2	4.1	yes	uniphasic		1.44	12.92
		iohexol 350	43.1 ± 7.0	4.8	yes	uniphasic		1.68	15.09
Liu [70]	18G	iopromide 370	47 ± 8	5.0/6.0	yes	uniphasic		1.85/2.22	17.39
		iopromide 370	44 ± 8	5.0/6.0	yes	uniphasic		1.85/2.22	16.28
		iopromide 370	36 ± 6	5.0/6.0	yes	uniphasic		1.85/2.22	13.32
Yang [71]	18G	iopamidol 370	30 – 60	4	yes	uniphasic		1.48	11.1 – 22.2
		iopamidol 370	60	4	yes	uniphasic		1.48	22.2
Tomizawa [72]	20 – 22G	iopamidol 370	49.3 ± 10.1	3.5 ± 0.7	no	uniphasic	37	1.3	18.24
		iopamidol 370	46.8 ± 7.6	3.3 ± 0.5	yes	uniphasic	37	1.22	17.32
		iopamidol 370	43.9 ± 9.6	3.6 ± 0.8	yes	uniphasic	37	1.33	16.24
Zheng [73]	18G	iodixanol 270	65.5 ± 11.1	5	yes	uniphasic		1.35	17.69
		iopromide 370	64.6 ± 12.9	5	yes	uniphasic		1.85	23.9
Lembcke [74]	18G	iopromide 370	30	5	yes	uniphasic		1.85	11.1
		iopromide 370	40	5	yes	uniphasic		1.85	14.8
		iopromide 370	50	5	yes	uniphasic		1.85	18.5
		iopromide 370	60	5	yes	uniphasic		1.85	22.2
		iopromide 370	70	5	yes	uniphasic		1.85	25.9

levels of the RCA with usage of an IDR ≥ 1.4gI/s [16, 45 – 47, 49, 54, 58], of which four studies report the lack of usage of a saline chaser [45, 46, 49, 58]. When no saline flush was applied, almost all publications report attenuation values of the RCA below a diagnostic level (< 325HU), stressing the importance of a saline chaser [44 – 46, 49, 58].

Discussion

The aim of this systematic review was to provide an update on the effect of different CM injection parameters on the attenuation in CCTA. A large variation regarding scan technique, patient characteristics and CM injection protocols was found. This heterogeneity makes it difficult to draw conclusions and stresses the need for studies in which such heterogeneity is avoided.

The findings in this systematic review confirm the need for an additional saline flush in a CM injection protocol. A saline flush pushes the tail of the injected CM bolus into the central blood volume thus utilizing CM that would otherwise remain behind in the injection tubing and peripheral veins [4]. Cademartiri et al. divided patients into two groups: group 1 (140 ml at 4 ml/s, no saline flush) and group 2 (100 ml at 4 ml/s followed by 40 ml of saline chaser at 4 ml/s) with an identical IDR (1.28gI/s). No significant differences in the attenuation of the coronary arteries were found [44]. As group 1 did not receive a saline flush, it is quite possible that some of the injected CM bolus was not dispensed into the central blood volume, leading to a decrease in the effective CM volume and subsequently to the non-significant differences in intracoronary attenuation.

The influence of CM concentration solely on attenuation has been an ongoing topic of interest. The majority of the included studies evaluating differences in CM concentrations did not find statistically significant differences in attenuation between groups [19, 52, 56, 58]. Some studies do attribute higher attenuation to higher CM concentrations [15, 16, 62]. Becker et al. conducted a double-blind multicenter randomized controlled trial, which randomized patients in 2 CM groups (iodixanol 320 mg/ml and iomeprol 400 mg/ml) in order to assess whether CM characteristics

affect diagnostic quality. In both groups 80 ml CM was injected at an identical injection rate of 5 ml/s [62]. A significant difference was found in coronary attenuation in favor of the 400 mg/ml group. They concluded that CM with a higher iodine concentration was beneficial to attenuation when administered at an identical injection rate and volume. However, administering different CM concentrations at an identical injection rate leads to differences in IDRs (320 mg/ml: 1.6gI/s vs. 400 mg/ml: 2.0gI/s). Therefore, the higher attenuation values in the 400 mg/ml group might not be attributed to the CM concentration solely, but rather to the calculated product of CM concentration and injection rate (e. g. higher IDR).

Comparable results are reported by Cademartiri et al. [15] who evaluated coronary attenuation in five different CM groups where both injection rate and CM volume were kept identical. Mean attenuation values were significantly lower in the lower CM group and higher in the highly concentrated CM group. Again, due to the use of an identical injection rate in both groups, the IDR varied significantly (1.2 to 1.6gI/s), rendering doubtful conclusions with regard to the sole superiority of higher CM concentrations. The results of this systematic review show diagnostic attenuation levels of the RCA in the vast majority of the included studies when IDR levels ≥ 1.4gI/s were used and suggest that IDR levels are easier to modify through usage of a large variety in flow rates rather than a limited variety in CM concentrations (e. g. 270 – 400 mg/ml).

Recent studies have confirmed the hypothesis that a CM with a lower iodine concentration provides attenuation levels equal to those obtained using a more highly concentrated CM when the IDR is kept identical [76, 77]. In both in vivo and phantom studies, comparison of protocols using different CM concentrations (varying between 240 – 400 mg/ml) established comparable intravascular enhancement patterns when the IDR and other CM- and scan-related factors were kept standardized. These findings are supported by a double-blind randomized controlled study, in which both the objective and the subjective image quality were evaluated with usage of different iodine concentrations (e. g. 240 mg/ml, 300 mg/ml and 370 mg/ml) while maintaining an identical IDR and total iodine load [78]. In addition, patient comfort and pain at the injection site with usage of flow rates varying 5.4 – 8.3 ml/s and incidence of contrast extravasation have been evaluated. No significant differences were found between groups regarding comfort, stress, and pain [78]. This study also shows that the reluctance towards the usage of higher flow rates as a possible cause for an increased incidence of extravasation due to increased injection pressures is merely based on hypothetical flow-related issues. In a recent feasibility study, the latter was confirmed in an in vitro and in vivo setup [79]. The results from these studies confirm in a standardized way that the injection with high flow rates does not have any negative side effects. No extravasation or flow-related problems were observed and the maximum injection pressure of 325psi was not reached. As CMs with a lower concentration are attractive due to their lower viscosity and, hence, lower injection pressure, these findings might stimulate a shift in paradigm towards clinical usage of CMs with lower iodine concentrations (e. g. 240 mg/ml) for individually tailored contrast protocols with subsequently higher flow rates.

Attenuation values cannot be attributed to a saline flush and the product of CM concentration and flow rate solely. Lembcke et al. assessed the effect of lower CM volumes on image quality in high-pitch CCTA [74]. Patients were randomly assigned to one of five groups with different CM volumes (e. g. 30 – 70 ml). The flow rate and CM concentration remained identical in all groups (5 ml/s and 370 mg/ml, respectively). As the volumes in all groups were different, the calculated TID is also different (varying between 11.1 g and 25.9 g). They reported significantly higher mean attenuation values in groups with higher CM volumes [74]. An increased total CM volume injected at the same flow rate leads to a prolonged injection duration, which increases the magnitude of vascular enhancement. Similarly, injection of a dedicated CM with higher flow rates affects both the magnitude and timing of contrast enhancement, leading to a shorter, earlier and higher peak enhancement and a proportional increase in vascular and parenchymal enhancement [1, 4, 11, 80, 81]. A short injection duration might be challenging and requires careful timing of CM bolus injection and data acquisition, especially in patients with abnormal hemodynamic parameters (e. g. irregular heart rate or low/high cardiac output) [74]. The authors recommend taking into account the patient's hemodynamic status, especially cardiac output, before imaging. Information regarding cardiac output has only been supplied in a very limited number of included publications [52, 64, 65, 68 – 70]. Body weight and BMI are known to have a substantial impact on vascular attenuation and time-to-peak in CTA [11, 82 – 84]. Many included publications evaluated the applicability of different body weight-adjusted CM injection or biphasic injection protocols with various outcomes. Seifarth et al. investigated whether individually tailored CM injection software resulted in higher vascular attenuation of coronary arteries compared to fixed injection protocols [55]. They evaluated a body weight adapted individualized CM injection software in comparison to two different standard injection protocols and found comparable or increased attenuation values in favor of the individualized CM injection software. However, besides overall mean attenuation of the coronary arteries between groups, an analysis for differences in attenuation values between weight classes was not performed. Another group evaluated the vascular attenuation of the coronary arteries as well as image quality and injection parameters within different weight classes by using identical body weight-adapted CM bolus injection software in comparison to a standardized injection protocol with fixed parameters [85]. Diagnostic attenuation in the entire coronary tree and a more homogeneous enhancement pattern between different weight groups was found with usage of the body weight-adapted injection software. The fixed injection protocol showed a large variation in the attenuation of the coronary arteries between different weight groups with higher attenuation levels in patients with a lower body weight and low attenuation levels in the heavier patients. These findings indicate suboptimal use of CM in different patient weight groups and show a clear benefit for individually tailored CM injection software in CCTA.

A thorough understanding of the influence of different injection parameters is considered a necessity for achieving the ultimate goal of individualized medicine. Disentangling the influence of patient-related parameters on attenuation and overall image

quality will be helpful in defining optimal bolus shaping in future injection protocols, hereby creating a doorway towards individualized CM application. Though a large variation in IDR is applied in CCTA in the daily clinical routine, there is no literature or consensus regarding the optimal IDR for the attenuation of the coronary arteries. The goal is to create a personalized CM injection protocol, where some patients (e. g. lower weight and/or length or heart rate ≤ 60 bpm) might require less CM with a different scan timing protocol than other patients (e. g. higher BMI or heart rate ≥ 60 bpm) to reach the same attenuation value. Research needs to be directed towards defining individualized optimal IDR tailored towards patient-related factors (e. g. weight, heart rate, cardiac output) with further incorporation of different scan and injection parameters into computer modeling software.

This study has several limitations. The study population inclusion criterion was set to a minimum of 30 patients. Furthermore, a limited number of prospective randomized trials are available on this topic. A known limitation in all systematic reviews is that studies with less favorable results have a tendency not to be published. A publication bias, therefore, cannot be ruled out. Another potential limitation is the heterogeneity of vendors and scanner types. Although technical advances have improved image quality substantially, image quality can vary between vendors and scanner types. Most studies provided only limited data concerning injection, scanning, and patient parameters. Not all corresponding authors of the included articles completed and sent back the questionnaire or provided additional information. Therefore, possible effects of patient level characteristics (e. g. BMI, cardiac output) could not be accounted for. Nevertheless, these factors have a significant impact in the clinical routine and should be addressed by individualized scan and CM injection protocols. Finally, most of the included studies were scanned with a tube voltage of 120 kV. The use of lower kV settings subsequently leads to a higher contrast enhancement, as a lower tube voltage translates into lower effective photon energy, bringing the latter closer to the K-edge of iodine (33.2keV) [86, 87]. Technical developments of the CT technique have made the use of lower tube voltage (kV) possible. Using the newest CT technology has made kV settings as low as 70 kV and 80 kV feasible, also for a broader range of patients, as a higher tube current (mA) is available. These technical developments add to the importance of adapting CM injections. As current technical developments are moving towards broad clinical application of lower kV settings, a substantial decrease in various determinant injection parameters (e. g. IDR, CM volume) is expected.

Conclusion

This systematic review shows that an adequate attenuation in the coronary arteries can be achieved with different CM injection protocols. Given the substantial variability between studies, it remains unclear which of the injection parameters is the most important determinant for adequate attenuation. It is highly likely that one parameter that combines multiple parameters (e. g. IDR) will be the most determinant factor for coronary attenuation in CCTA protocols. Research needs to be directed towards unraveling the influence of injection parameters and defining individualized optimal IDRs tailored to patient-related factors. This will make it possible to offer a CM injection protocol with applicability of a broad variety of injection and scan-related parameters tailored to each individual patient.

LIST OF ABBREVIATIONS

CCTA	Coronary Computed Tomographic Angiography
CM	Contrast Media
TID	Total Iodine Dose
HU	Hounsfield Units
IDR	Iodine Delivery Rate
MDCT	Multidetector Computed Tomography
BMI	Body Mass Index
RCA	Right Coronary Artery
LAD	Left Anterior Descending artery
Cx	Circumflex artery

Conflict of Interest

No conflict of interest has been declared by the author(s).

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