Clinical Applications of Conebeam CTP Imaging in Cerebral Disease: A Systematic Review

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ABSTRACT

BACKGROUND: Perfusion imaging with multidetector CT is integral to the evaluation of patients presenting with ischemic stroke due to large-vessel occlusion. Using conebeam CT perfusion in a direct-to-angio approach could reduce workflow times and improve functional outcome.

PURPOSE: Our aim was to provide an overview of conebeam CT techniques for quantifying cerebral perfusion, their clinical applications, and validation.

DATA SOURCES: A systematic search was performed for articles published between January 2000 and October 2022 in which a conebeam CT imaging technique for quantifying cerebral perfusion in human subjects was compared against a reference technique.

STUDY SELECTION: Eleven articles were retrieved describing 2 techniques: dual-phase ($n = 6$) and multiphase ($n = 5$) conebeam CTP.

DATA ANALYSIS: Descriptions of the conebeam CT techniques and the correlations between them and the reference techniques were retrieved.

DATA SYNTHESIS: Appraisal of the quality and risk of bias of the included studies revealed little concern about bias and applicability. Good correlations were reported for dual-phase conebeam CTP; however, the comprehensiveness of its parameter is unclear. Multiphase conebeam CTP demonstrated the potential for clinical implementation due to its ability to produce conventional stroke protocols. However, it did not consistently correlate with the reference techniques.

LIMITATIONS: The heterogeneity within the available literature made it impossible to apply meta-analysis to the data.

CONCLUSIONS: The reviewed techniques show promise for clinical use. Beyond evaluating their diagnostic accuracy, future studies should address the practical challenges associated with implementing these techniques and the potential benefits for different ischemic diseases.

ABBREVIATIONS: CBCT = conebeam CT; ICC = intraclass correlation coefficient; LVO = large-vessel occlusion; PBV = parenchymal blood volume; r = relative

Perfusion imaging with multidetector CT has become part of the standard diagnostic evaluation for patients presenting with symptoms of acute ischemic stroke.[1] In patients beyond the conventional treatment time windows, it is used to select patients who may benefit from IV thrombolysis and/or endovascular therapy.[2-4] Time from symptom onset to treatment has been shown to be one of the most significant modifiable factors affecting clinical outcome.[5-7]

For patients suspected of having a cerebral large-vessel occlusion (LVO), studies have investigated whether the time to treatment can be reduced by transferring the patients directly to the angiosuite and bypassing the initial stroke triage in the emergency department. Considerable reductions in door-to-puncture times have been demonstrated with a direct-to-angio approach. These studies focused on the ability of using conebeam CT (CBCT) to detect intracerebral hemorrhage and an LVO.[8-14]

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New CBCT perfusion techniques, such as dual-phase[15] and multiphase[16] CBCT imaging, have also been recently introduced and found to be able to detect perfusion deficits in patients with an LVO. For a reliable evaluation of perfusion deficits in the late time window, CBCTs must, however, have a diagnostic accuracy and precision comparable with those of multidetector CTP imaging.

This systematic review provides an overview of CBCT techniques for quantifying cerebral perfusion techniques, their clinical applications, and validation with other reference techniques.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Online Supplemental Data).[17] This systematic review and the corresponding search strategy have been registered in the PROSPERO registry (registration number: CRD42021243288). The review and search strategy were formulated using the Population, Intervention, Comparison, and Outcomes framework. Due to the heterogeneity in the methodology, interventions, and outcomes of the retrieved studies, they could not be grouped. Therefore, the studies were narrowed down to those investigating CBCT techniques for cerebral perfusion imaging. Furthermore, due to the heterogeneity in the studies included in the review, no meta-analysis was performed. Descriptions of the techniques, their applications, and correlations with the reference techniques were reported.

Literature Search

EMBASE, PubMed, the Cochrane Library, and the Cumulative Index of Nursing and Allied Health were searched for eligible studies on CBCT perfusion imaging techniques. The search was performed with the help of Medical Subject Heading terms, free text, and Boolean operators. Additional articles were retrieved through cross-checking references in the relevant literature. The full search strategy can be found in the Online Supplemental Data. Studies published before January 2000 were excluded because the technology before that time is considered outdated.

Titles and abstracts of the studies were independently reviewed by 2 authors (A.H.A.Z.A., W.D.M.) by means of Rayyan software (Rayyan Systems).[18] The reviewers were blinded to the authors and journal titles. Items in which there was disagreement were discussed by the 2 reviewers to reach a consensus for inclusion. If consensus could not be reached, adjudication was provided from a third reviewer (R.P.H.B.).

Selection Criteria

Articles including a CBCT imaging technique for quantifying perfusion in the brain were eligible. The CBCT techniques had to be compared with another perfusion imaging technique using a different modality. Furthermore, the studies were required to report the correlations between the CBCT technique and the reference technique. The selected articles included only human subjects and were not limited to a language. Online translation services were used to translate studies in languages other than English. Exclusion criteria were studies with $<$10 subjects, case reports, case series studies, review articles, conference abstracts, letters to the editors, commentaries, and studies without full text availability.

Data Extraction and Quality Assessment

The study details from the relevant articles were extracted using a predefined form and categorized according to the CBCT perfusion imaging technique. We extracted the following data: study year, study design, number of patients, diagnoses, CBCT technique, reference technique, the measured perfusion parameters, and correlations among them. Data were collected using the Rayyan software.[18] The Quality Assessment of Diagnostic Accuracy Studies tool[19] was used for appraisal of quality and the risk of bias and was conducted by 1 reviewer (A.H.A.Z.A.).

Results and Description of Techniques

The search resulted in 6165 records, of which 993 were duplicates. After detailed evaluation of the titles and abstracts, 355 articles were selected for full-text assessment. Of these articles, 52 were excluded due to lack of comparison with a reference technique, 291 were excluded because of different outcomes, and 5 were excluded because the measurements were performed in different organs. Four articles were retrieved through cross-checking references in the relevant literature. Eleven articles were found to be eligible for inclusion. An outline of the review process can be found in the Online Supplemental Data.

Six of the 11 articles investigated dual-phase CBCT perfusion in patients with cerebral ischemia. The 5 remaining studies investigated multiphase CBCT perfusion, 2 of which were in patients undergoing carotid artery stent placement, and 3 were in patients with acute ischemic stroke due to LVO. The included study characteristics and the quality and risk of bias appraisal of the included studies are shown in the Online Supplemental Data. Most of the studies in this review demonstrated little-to-no concern about the applicability and risk of bias.

CBCT Perfusion Imaging

Dual-Phase CBCT Perfusion. Dual-phase CBCT perfusion is a 3D technique from which the perfusion parameter parenchymal blood volume (PBV) is derived. These perfusion maps are derived by acquiring two 3D volumes[15] and are based on a single compartment model.[20,21]

First, an initial noncontrast mask volume is acquired, after which injection of a contrast medium is started by using a prolonged injection protocol that floods the arteries, tissues, and veins with contrast. On the basis of DSA observation between the scans, the fill run is manually started when opacification of the veins becomes visible to ensure the presence of a steady state of contrast in the entirety of the image for the duration of the acquisition. The acquisition is illustrated in the Online Supplemental Data.

The images are derived by means of postprocessing in which the mask and fill runs are reconstructed separately.[15] First the 2 volumes are coregistered, after which the noncontrast mask volume is subtracted from the contrast-enhanced volume. An algorithm is then applied to segment out air and bone. Afterward, the steady-state arterial input function is automatically calculated.

The image volume is normalized by applying a final scaling. To reduce pixel noise, a smoothing filter is applied.

Calculation of PBV requires the time curves for contrast in tissue, artery, and vein, which is not possible with a CBCT. Using the steady-state method, PBV can then be inferred to be equal to multidetector CT-derived CBV. However, PBV has been shown to be a composite perfusion parameter, exhibiting properties similar to both CBV and CBF.[22]

Clinical Applications. In this systematic review, 6 prospective studies were retrieved that investigated the use of dual-phase CBCT perfusion for the assessment of cerebral hemodynamic status in 106 patients. Five studies investigated patients with signs of acute ischemic stroke, and 1 study investigated patients with delayed cerebral ischemia after aneurysmal SAH.

In patients with acute cerebrovascular signs, all 5 studies compared CBCT CBV with CTP CBV. Struffert et al[23-25] performed 3 prospective studies in 48 patients. CTP was performed before treatment in all studies, and PBV was calculated after treatment with a time difference between the 2 acquisitions from 95 minutes to 24 hours. Correlations between CBCT CBV and CTP CBV ranged from $r = 0.72$ to $r = 0.90$. Two studies prospectively studied both PBV and CTP CBV in 32 patients with signs of cerebrovascular ischemia and reported comparable good correlations between the 2 techniques.[26,27] Furthermore, no treatment was performed in the time interval between the scans.

Kamran et al[22] compared relative (r) PBV (rPBV = right PBV/left PBV) measurements with rCBF derived from MRI-PWI and rCBV in 26 patients with delayed cerebral ischemia after aneurysmal SAH. Delayed cerebral ischemia was defined as clinical deterioration lasting ≥2 hours without imaging evidence of rebleeding or hydrocephalus and no other medical causes. Clinical deterioration occurred an average of 7 days after aneurysmal SAH. Moderate-to-good correlations were reported between rPBV and MRI-PWI rCBF ($r = 0.85$ and $r = 0.78$), and rPBV versus MRI-PWI rCBV ($r = 0.72$ and $r = 0.69$) was reported for cortical and subcortical voxels of interest, respectively. The average time between the scans was 124 minutes.

Multiphase CBCT Perfusion. Multiphase CBCT perfusion is a technique in which perfusion parameters, such as CBV, CBF, MTT, and TTP, are derived by acquiring multiple sequential volumes after injection of contrast. Time-density curves are then generated throughout the brain tissue to calculate parametric perfusion maps.

Acquisition is based on the work of Royalty et al.[28] Before contrast injection, 2 high-speed baseline scans (clockwise and counterclockwise) are performed to obtain mask images. A contrast bolus is then injected, after which 7 or 8 high-speed bidirectional scans are obtained. The average rotation time is approximately 5 seconds, with 1 second between the rotations, resulting in a sampling time of 6 seconds. A motion-correction algorithm based on mutual information is used to decrease movement artifacts.[29,30] The acquisition protocol is outlined in the Online Supplemental Data.

After manual selection of the arterial input function, parametric perfusion maps of TTP, CBV, CBF, and MTT are calculated, similar to CTP by means of a modified deconvolution algorithm.[16,31,32]

Clinical Applications. Five studies were retrieved in this review that prospectively compared multiphase CBCT perfusion with MR perfusion or CTP. A total of 69 patients were included.

Lin et al[33] evaluated the feasibility of quantifying oligemia in 10 patients with carotid stenosis before treatment. Relative and absolute values of TTP, MTT, CBF, and CBV were compared with those of MR perfusion. For the relative values, the correlations were moderate-to-good: rTTP ($r = 0.75$), rCBF ($r = 0.79$), and rCBV ($r = 0.50$). For the absolute measurements, the correlations were poor-to-moderate: TTP ($r = 0.56$), MTT ($r = 0.47$), CBF ($r = 0.43$), and CBV ($r = 0.47$). No correlations were reported for rMTT between CBCT and MR perfusion.

Chen et al[34] evaluated the feasibility of using CBCT to monitor cerebral hemodynamics during carotid artery stent placement in 13 patients. Relative and absolute TTP, CBV, MTT, and CBF were measured before and after treatment by both MR perfusion and CBCT. They reported no correlations in the absolute parameters. Before stent placement, there was moderate-to-good correlation for rTTP ($r = 0.58$) and rCBF ($r = 0.73$). After stent placement, none of the parameters were correlated between CBCT and MR perfusion.

Struffert et al[35] investigated the feasibility and qualitative comparability of multiphase CBCT perfusion in 12 patients with LVO and perfusion mismatch presenting beyond 4.5 hours of symptom onset. The scans with CBCT and MR perfusion were obtained within 30 minutes of each other. The results were evaluated by 2 reviewers (A and B). For reviewer A, the correlation was moderate for CBV ($r = 0.49$) and good for CBF ($r = 0.97$), MTT ($r = 0.96$), and TTP ($r = 0.96$). For reviewer B, the correlation was poor for CBV ($r = 0.40$) and good for CBF ($r = 0.98$), MTT ($r = 0.95$), and TTP ($r = 0.97$).

Kurmann et al[36] prospectively compared preinterventional volumes of ischemic core, penumbra, and mismatch between multiphase CBCT perfusion and CTP in 20 patients with LVO. Scans were obtained with a maximum of a 2-hour delay in between. The infarct core threshold was set at rCBF <30% and rCBF <45% for CTP and multiphase CBCT, respectively. The penumbra threshold was set at a time-to-maximum of >6 seconds. They reported good ($r^2 = 0.84$) correlations for conventional rCBF (<30%) and multiphase CBCT rCBF (<45%). The correlation was poor ($r^2 = 0.33$) for mismatch volumes and moderate ($r^2 = 0.57$) for penumbra volumes.

Ortega-Gutierrez et al[37] prospectively compared perfusion maps between multiphase CBCT perfusion and CTP in 14 patients with acute ischemic stroke due to LVO. The median time between the scans was 42 minutes. The comparison was made using 3 methods: Method 1 was based on placing matched ROIs in the anterior circulation, method 2 was based on placement of matched ROIs in the 10 areas of the MCA corresponding to the ASPECTS,[38] and method 3 was based on manual drawing of ROIs in areas with visually apparent perfusion abnormalities. For the first method, the correlation was good (intraclass correlation coefficient [ICC] = 0.77) for MTT and moderate (ICC = 0.58, ICC = 0.65, ICC = 0.52) for CBF, CBV, and time-to-maximum/TTP, respectively. For the second method, the correlation was poor (ICC = 0.32) for time-to-maximum/TTP, and moderate (ICC = 0.51, ICC = 0.57, ICC = 0.62) for CBF, CBV, and MTT, respectively. For the third method, the correlation was poor (ICC = 0.15) for time-to-maximum/TTP, moderate (ICC = 0.70) for CBF, and good (ICC = 0.83, ICC = 0.95) for MTT and CBV, respectively.

DISCUSSION

This systematic review provides an overview of the currently available CBCT techniques to image tissue perfusion in the brain. We identified 11 studies based on a dual-phase ($n = 6$) or multiphase ($n = 5$) CBCT perfusion imaging techniques. Moderate-to-good correlations were reported between the CBCT techniques and the reference techniques; however, most of the studies demonstrated a large time interval between the scans and included small heterogeneous cohorts.

Studies of endovascular therapy in the late time window (6–24 hours after stroke onset) and intravenous thrombolysis[2-4] have relied on CTP or multimodal MR imaging (diffusion-weighted and perfusion-weighted imaging) to identify patients with small ischemic core volumes and relatively large penumbra volumes. The studies in this review suggest that CBCT perfusion imaging can be used for assessing cerebral ischemic disease, either as adjuncts to conventional imaging for intraoperative monitoring or a substitute for conventional CTP in a direct-to-angio approach. A recent meta-analysis of the direct-to-angio approach demonstrated its safety and effectivity in decreasing door-to-treatment times.[39] However, none of the included studies in this review investigated the diagnostic accuracy of CBCT perfusion imaging in terms of quantitative assessment of perfusion or its ability to distinguish core from penumbra in acute ischemic stroke.

The studies in this review that investigated dual-phase CBCT perfusion demonstrated the feasibility of this technique to provide real-time assessment of the perfusion parameter PBV and reported good correlations between PBV and CTP CBV. Furthermore, it has been demonstrated that PBV could potentially predict final infarct volume in patients with stroke.[25] On the other hand, PBV is not yet fully understood as a perfusion parameter and has been demonstrated to be a composite parameter, incorporating both CBV and CBF.[22] The implications for its ability to select patients for revascularisation therapy are, therefore, unknown. Future studies should focus on investigating the comprehensiveness of PBV and its clinical applicability.

Multiphase CBCT perfusion is a technique that can assess multiple perfusion parameters.[40,41] However, the limited temporal resolution of CBCTs may affect the quantification of the perfusion parameters.[42-45] The studies in this review have demonstrated the feasibility of this technique in patients with chronic ($n = 2$) and acute ($n = 3$) ischemia. The reported correlations between CBCT and MR perfusion ranged from poor to good for all perfusion parameters, but in some instances, they did not correlate at all.[33-35] In studies investigating the technique in patients with stroke with LVO, weak correlations for penumbra and mismatch volumes from CBCT and CTP were reported,[36] and weak-to-good correlations were reported between perfusion parameters from CBCT and CTP.[36,37] Multiphase CBCT perfusion demonstrates promising accuracy and applicability in patients with stroke with LVO; however, the current evidence is limited. Future studies should aim to investigate the diagnostic accuracy and include large homogeneous cohorts, a standardized acquisition protocol, and comparison with a criterion standard, such as PET perfusion imaging.

Both reported CBCT perfusion techniques require a lower dose of contrast and radiation than conventional CT for acquiring the same data. A multidetector CT stroke protocol consists of perfusion imaging, noncontrast CT, and angiographic imaging, resulting in a total dose of approximately 8–9 mSv for an entire evaluation.[46-48] Multiphase CBCT perfusion requires a total effective radiation dose of 4.6 mSv.[33-35] Furthermore, with this technique, additional reconstructions can be applied in the same acquisition only to the mask runs and only to the fill runs to provide soft-tissue and dynamic angiographic imaging, respectively.[23] Therefore, a single multiphase CBCT acquisition could provide data that are analogous to a full multidetector CT stroke protocol for around half the radiation dose. A dual-phase CBCT scan provides PBV measurements, in addition to large-vessel and soft-tissue reconstructions, which could reliably assess the patency of large vessels, the presence of vasospasms, and the presence of intracranial hemorrhage.[22,49]

While the direct-to-angio approach has proved safe and feasible in reducing door-to-puncture times, it faces numerous limitations with regard to practicalities and applicability. In patients with acute ischemic stroke, the initial triage is aimed at ruling out intracerebral hemorrhage and confirming LVOs. Prolonged selection protocols identify only a minority of patients who may not benefit from treatment, leaving most at risk.[8] On the other hand, simplifying the selection process may increase the number of patients undergoing angiography who would not benefit from the procedure.[9] This potential disadvantage should be carefully considered when implementing measures to reduce complexity. Furthermore, standardized clinical scales must be introduced and in-hospital organization should be realized to optimize the benefit of such an approach and achieve better outcomes.[50]

This selected literature has limitations. First, the heterogeneity between and within the techniques, the C-arm systems, and postprocessing methods made it difficult to draw conclusions and impossible to apply meta-analysis to the data. Second, a large heterogeneity exists with regard to the terminology; numerous terms could be used to describe the same technique/system. Last, none of the studies in this review investigated the diagnostic accuracy of the CBCT techniques against conventional methods.

CONCLUSIONS

The CBCT techniques in this review demonstrate the potential for implementation in clinical practice. Dual-phase CBCT perfusion could be used as an adjunct to conventional diagnostic methods, potentially improving overall outcome and safety, with the advantage of reduction of contrast medium and radiation dose. However, it does not provide a full assessment of brain perfusion parameters, and the comprehensiveness of PBV remains unclear. Multiphase CBCT perfusion provides an assessment of multiple brain perfusion parameters and could reduce door-to-puncture times substantially and improve functional outcome in a direct-to-angio approach. On the other hand, multiphase CBCT has low temporal resolution, and its parameters did not consistently correlate with the reference technique. In addition to investigating their performance and diagnostic accuracy, future studies should address the practical challenges associated with implementing these techniques and the potential benefits for different ischemic diseases.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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