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FULL PAPER

Evaluation of the liver with virtual non-contrast: single institution study in 149 patients undergoing TAVR planning

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Objective: To evaluate accuracy of virtual-non-contrast images (VNC) compared to true-unenhanced-images (TNC) for evaluation of liver attenuation acquired using spectral-detector CT (SDCT).

Methods: 149 patients who underwent multiphase transcatheter-aortic-valve-replacement (TAVR) SDCT-examinations [unenhanced-chest (TNC), CT-angiography chest (CTA-chest, early arterial-phase) and abdomen (CTA-abdomen, additional early arterial-phase after a second injection of contrast media)] were retrospectively included. VNC of CTA-chest (VNC-chest) and CTA-abdomen (VNC-abdomen) were reconstructed and compared to TNC. Region of interest-based measurement of mean attenuation (Hounsfield unit, HU) was applied in the following regions: liver, spleen, abdominal aorta and paraspinal muscle.

Results: VNC accuracy was high in the liver, spleen, abdominal aorta and muscle for abdomen-scanning. For the liver, average attenuation was 59.0 ± 9.1 HU for TNC and 72.6 ± 9.5 HU for CTA-abdomen. Liver attenuation

in VNC-abdomen (59.1 ± 6.4 HU) was not significantly different from attenuation in TNC ($p > 0.05$). In contrast, VNC was less accurate for chest-scanning: Due to the protocol, in CTA-chest no contrast media was present in the liver parenchyma as indicated by the same attenuation in TNC (59.0 ± 9.1 HU) and CTA-chest (58.8 ± 8.9 HU, $p > 0.05$). Liver attenuation in VNC-chest (56.2 ± 6.4 HU, $p < 0.05$) was, however, significantly lower than in TNC and CTA-chest implying an artificial reduction of attenuation.

Conclusion: VNC performed well in a large cohort of TAVR-examinations yielding equivalent mean attenuations to TNC; however, application of this technique might be limited when no or very little contrast media is present in parenchyma, more precisely in an early arterial-phase of the liver.

Advances in knowledge: This study showed that VNC can be reliably applied in cardiac protocols when certain limitations are considered

INTRODUCTION

In clinical imaging, unenhanced CT acquisitions of the upper abdomen are rather rare. Most commonly contrast-enhanced CT acquisitions are applied. Depending on the clinical question, protocols can be specialized and include several contrast phases and also unenhanced acquisitions,¹ e.g. for evaluation of hepatocellular carcinoma,² vessel pathologies and unknown bleeding,^{3,4} as well as adrenal lesions.⁵ Quantitative evaluation of liver attenuation, e.g. for imaging-based diagnosis of fatty liver disease, is also dependent on unenhanced acquisitions.⁶⁻⁸ However, it needs to be considered, that adding

additional unenhanced examinations also increases radiation exposure.⁹⁻¹¹

Dual-energy CT solutions can be divided in tube- and detector-based systems. Clinically available are several tube-based solutions, but only one detector-based system, usually referred to as spectral-detector CT (SDCT). This scanner uses one X-ray source and a dual-layer detector; photons with lower energies are detected at the upper, while photons with higher energies are detected at the lower layer.^{12,13}

Figure 1. Flowchart demonstrates study inclusion process undergone by patients with TAVR examinations on SDCT. HU, Hounsfield unit; LAI, Liver attenuation index; SDCT, spectral-detector CT; TAVR, transcatheter aortic valve replacement.

Virtual non-contrast or virtual-unenhanced images (VNC) made available by dual-energy CT represent a potential way to reduce the amount of CT scans as separation of low and high energy data allows for accurate identification and removal of iodine.^{3,12} Studies focusing on dedicated abdominal protocols, including arterial, portal-venous and/or urographic phase examinations, and/or phantoms have shown attenuation and image noise in VNC comparable to true unenhanced scans (TNC), but this has not been shown for (SDCT) into a larger patient cohort and/or focus on the liver.^{3,14–16}

CT examinations prior to transcatheter-aortic-valve-replacements (TAVR) are increasingly applied, including unenhanced scans of the chest and CT angiography (CTA) of chest and abdomen.^{17,18} This dedicated cardiac examination also depicts upper abdominal organs, such as the liver, but differs in scan and contrast media injection protocols. Still, VNC has not been investigated in these patients and for these dedicated contrast phases. In multiphase TAVR planning SDCT examinations, we therefore investigated accuracy of VNC from contrast-enhanced scans for evaluation of liver attenuation by comparing them to true unenhanced acquisitions.

METHODS AND MATERIALS

This retrospective study was approved by the institutional-review-board and the standards of the Health-Insurance-Portability-as well as Accountability-Act were followed. Informed written consent under Code-of-Federal-Regulations (title 45, §46.116d)

was waived. Criteria for general inclusion were (i) scans from a clinical spectral-detector CT system (IQon, Philips Healthcare) between May 2017 and September 2018 and (ii) patient age ≥ 18 years. For the final analyses, 149 patients were included fulfilling following additional criteria: (i) TAVR planning examinations of patients with severe aortic stenosis: unenhanced chest (TNC), CT angiography chest (CTA-chest, early arterial-phase), and CTA abdomen (CTA-abdomen, additional early arterial-phase after a second contrast media injection 120s after CTA-chest); examinations were always applied in this order, (ii) at least two-thirds of the spleen as well of the liver depicted in all three acquisitions, and (iii) complete imaging data set of all three acquisitions (Figure 1).

Imaging protocol

For the unenhanced chest scan, imaging was performed with a prospectively ECG-triggered axial scan (Step & Shoot) at 78% of the RR-interval and the following further scan parameters: tube-voltage 120 kVp, tube-current automatically adapted to patient size [DoseRight, ACS, Philips Healthcare; reference values for tube current: 250 mAs, and CT dose index (CTDIvol): 16.0 mGy], collimation 64×0.625 mm and rotation time 0.33 s. Data were reconstructed using iterative reconstruction (iDose,⁴ level 3, Philips Healthcare) with a slice thickness of 2 mm and 50% overlap. For CTA-chest examinations, 25 ml of iodinated contrast agent (Optiray 350, Guerbet) were administered through an antecubital vein. A retrospective ECG-gated helical scan was started using bolus-tracking: a region of interest (ROI) was placed in the left atrium and scan was initiated after a threshold of 60 Hounsfield units (HUs) was reached. Scan parameters included tube-voltage of 120 kVp, tube-current automatically adapted to patient size (DoseRight, ACS, Philips Healthcare, reference values for tube current: 565 mAs, and CTDIvol: 51.0 mGy), collimation 64×0.625 mm, rotation time 0.33 s and pitch 0.2. Data were reconstructed using iterative reconstruction (iDose,⁴ level 3, Philips Healthcare) and at a RR-interval equal to 78% and a slice thickness of 2 mm ($n = 116$) or 0.9 ($n = 33$) with 50% overlap. For CTA-abdomen another 25 ml of contrast agent was administered 120s after the chest scan, so effectively patients received a split-bolus, totaling 50 ml of contrast agent. The scan was started using bolus-tracking with a ROI in the descending aorta when attenuation increased 10 HU over the baseline. This threshold was chosen, as the earlier contrast-enhanced CTA-chest scan had already been conducted. Therefore, baseline attenuation within the descending aorta was higher as compared to routine protocols and varied between patients due to individual differences in circulation. Scan parameters were tube-voltage of 120 kVp, tube-current automatically adapted to patient size and anatomy and modulated based on patient anatomy (DoseRight, 3D-DOM, Philips Healthcare, reference values for tube current: 116 mAs, and CTDIvol: 10.0 mGy), collimation 64×0.625 mm, rotation time 0.5 s and pitch 1.02. Data were reconstructed using iterative reconstruction (iDose,⁴ level 3, Philips Healthcare) with a slice thickness of 2 mm with 50% overlap. VNC were created from CTA-chest and CTA-abdomen data using the vendor's dedicated spectral reconstruction algorithm (Spectral B, level 3, Philips Healthcare). VNC-chest images were reconstructed with a slice thickness of 2 ($n = 116$) and 0.9 mm ($n = 33$); for both

with 50% overlap. VNC-abdomen images were reconstructed with a slice thickness of 2 mm with 50% overlap.

Objective analysis

Objective analysis was carried out on axial images by applying circular ROI of at least 500 mm² to measure the mean of attenuation measured in HU. ROI size could possibly be reduced to avoid unrepresentative tissue. ROI were first placed in CTA-abdomen (anatomical identification and structure delineation was most accurate here) and subsequently copied to TNC and CTA-chest as well as VNC-chest and VNC-abdomen within the vendor's proprietary image viewer (IntelliSpace Portal v. 9, Philips Healthcare). Due to respiratory motion, ROI positions could differ for image sets derived from different acquisitions. To minimize any mismeasurements from differences in ROI positioning, the objective reader used screenshots of each ROI in CTA-abdomen images to match placement in the other image sets. Two ROI on different levels were placed in the right liver lobe, left liver lobe, spleen, and abdominal aorta. One single ROI was placed in paraspinal muscle, resulting in a total of 6,705 ROI (9 ROI in 5 reconstructions for each of the 149 patients). When two ROI were placed in the same anatomical location, the measured values were averaged together. The results from the four ROI from the right and left liver lobes were also averaged to obtain results for the entire liver. Individual differences in the mean attenuation of each structure were determined by computing the difference in HU-values between VNC and TNC. As suggested earlier,^{3,16} individual differences in attenuation of less than 10 HU were considered clinically acceptable and equivalent to TNC.

Statistical analysis

JMP Software was applied for any statistical testing (v. 14, SAS Institute). Quantitative results are presented as mean $\pm$ SD.

Shapiro-Wilk test was used to test for normal distribution. Wilcoxon-test signed-rank test was used for testing of any difference between attenuation in TNC and VNC. Statistical significance was defined as $p < 0.05$.

RESULTS

The 149 included patients comprised 69 females and 80 males with a mean age of 80.4 ± 9.5 years, ranging from 56 to 99 years. Only 5 of 149 patients showed signs of liver steatosis (liver attenuation < 40 HU¹⁹ and/or liver attenuation index < -10 HU^{20,21}, Figure 1).

Objective assessment

The Shapiro-Wilk test did not show normal distribution for values in all assessed groups ($p < 0.05$). Mean attenuation values of VNC and TNC have been similar in all analyzed structures, partly with and without significant differences, as can be seen in Table 1 in more detail (also see Figures 2–4). Smallest mean attenuation differences could be seen in the liver between VNC-abdomen and TNC of only 0.1 ± 6.7 HU (Table 1, $p > 0.05$).

In CTA-chest, no contrast media appeared to have arrived in the liver at the time of the scan as indicated by the same attenuation in TNC (59.0 ± 9.1 HU) and CTA-chest images (58.8 ± 8.9 HU, $p > 0.05$). However, when VNC images were created from CTA-chest data, attenuation differences in the liver between VNC-chest and TNC were statistically significant with (-2.8 ± 5.8 HU, $p = 0.005$; Table 1) implying VNC-chest falsely removed attenuation and regions were mistakenly identified as containing iodine. The results were similar when the right and left liver lobe were evaluated separately and in muscle; for each structure little to no contrast media was detected in CTA-chest images as evidenced

Table 1. Attenuation values of the examined upper abdominal structures

	Whole liver	Right liver lobe	Left liver lobe	Spleen parenchyma	Abdominal aorta	Muscle
TNC	59.0 ± 9.1	56.6 ± 10.3	61.5 ± 8.7	48.2 ± 6.5	41.4 ± 6.2	37.6 ± 14.3
VNC-chest	56.2 ± 8.0	55.1 ± 8.8	57.3 ± 8.0	48.7 ± 5.4	41.9 ± 7.6	36.9 ± 11.1
VNC-abdomen	59.1 ± 6.4	59.3 ± 6.9	58.8 ± 6.3	50.9 ± 4.8	40.9 ± 6.0	38.9 ± 10.1
CTA-chest	58.8 ± 8.9	56.4 ± 9.9	61.2 ± 8.7	58.2 ± 14.6	168.3 ± 85.4	39.3 ± 12.6
CTA-abdomen	72.6 ± 9.5	69.7 ± 9.8	75.6 ± 9.7	88.7 ± 20.1	139.1 ± 65.8	42.5 ± 11.2
<i>Differences of mean values of</i>						
VNC-chest & TNC	-2.8	-1.5	-4.2	0.5	0.5	-0.7
VNC-abdomen & TNC	0.1	2.7	-2.7	2.7	-0.5	1.3
<i>Individual differences of</i>						
VNC-chest & TNC < 10 HU	92.6%	87.9%	89.2%	83.2%	75.1%	76.5 %
VNC-abdomen & TNC < 10 HU	92.3%	84.5%	87.9%	81.9%	83.9%	75.8 %
<i>p-values</i>						
VNC-chest vs TNC	$p = 0.005$	$p > 0.05$	$p < 0.001$	$p > 0.05$	$p > 0.05$	$p > 0.05$
VNC-abdomen vs TNC	$p > 0.05$	$p = 0.007$	$p = 0.002$	$p < 0.001$	$p > 0.05$	$p > 0.05$

CTA, CT angiography; HU, Attenuation in HU; TNC, true non-contrast; VNC, virtual non-contrast.

Figure 2. Box-plot diagram displaying attenuation in liver, spleen and abdominal aorta in TNC, VNC from CTA of the chest (VNC-chest), CTA-chest, VNC-abdomen from CTA of the abdomen and CTA-Abdomen. VNC effectively removes contrast media and displays attenuation values comparable to TNC for all three structures. CTA, CT angiography; VNC, virtual non-contrast; TNC, true non-contrast.

by similar attenuation in TNC and CTA-chest images (differences < 2 HU, Table 1, $p > 0.05$) but still VNC-chest reduced attenuation to values lower than TNC (which was significant for the left liver lobe). Detailed results can be seen in Table 1. However, the phenomenon of potentially falsely decreased attenuation in VNC compared to TNC did not occur when contrast media was present in structures in CTA-chest images, e.g. spleen and abdominal aorta (Table 1).

Individual differences in attenuation in VNC-chest and VNC-abdomen compared to TNC were < 10 HU for the entire liver, right and left liver lobe, spleen, abdominal aorta and muscle, for most analyzed structures (ranging between 75.1 and 92.6%, Table 1). More detailed results can be seen in Table 1.

DISCUSSION

This study evaluated the accuracy of VNC images derived from spectral-detector CT data in comparison to TNC for attenuation evaluation of the liver in a cohort of TAVR planning patients. VNC-abdomen effectively removed iodine and showed very similar image characteristics to TNC in liver indicating that it is a valuable tool that could potentially replace unenhanced CT examinations for liver assessment. Still, in VNC-chest we noted that if no contrast media was present in the liver, VNC attenuation was significantly lower than in TNC creating potentially falsely low attenuation values. This trend was pronounced when the liver was considered in its entirety but could also be appreciated in the right and left liver lobe separately as well as in muscle. In structures that already showed a certain amount of contrast media, VNC-chest worked well and did not falsely reduce attenuation beyond values displayed in TNC images. Although, this difference was relatively small this potential restriction—false results from contrast removal in scans with very low enhancement—should be considered for application in clinical practice whenever attenuation values are used.^{5,8,19–22}

For abdominal imaging, accuracies of VNC have been described as reliable with relatively low differences in attenuation

Figure 3. Effective removal of contrast media by VNC of CTA of the chest and abdomen offering comparable visual impression compared to TNC. Axial CT images in soft tissue window settings (window level: 60, window width: 350) of the upper abdomen in a 56-year-old male receiving TAVR planning examination. TNC, true non-contrast; CTA, CT angiography; TAVR, transcatheter aortic valve replacement; VNC, virtual non-contrast.

Figure 4. 84-year-old female patient with signs of liver steatosis in TNC images shown by liver attenuation <40 HU and LAI <-10 HU. The same diagnosis is also possible in VNC of CT angiography of the chest and abdomen. To TNC comparable attenuation values are displayed that also meet the criteria of liver steatosis by liver attenuation and LAI. Axial CT images in soft tissue window settings (window level: 60, window width: 350) of the upper abdomen (a) without and (b) with placed ROI. HU, Hounsfield unit; LAI, liver attenuation index; ROI, region of interest; TNC, true non-contrast; VNC, virtual non-contrast.

compared to TNC.^{3,8,16,23,24} Two studies investigating in VNC in SDCT examining the entire abdomen with less focus on the liver showed in 75–80% of the measurements differences <10 HU ($n = 46$ and 62 patients).^{3,16} This is in line with our results that showed differences <10 HU between VNC and TNC attenuation in 84.2% of the measurements, so application of VNC for imaging of the liver appears feasible also in cardiac scans and injection protocols. In general, but especially VNC-abdomen has been more accurate in depiction of liver attenuation. These further improvements might be explained as we used a commercially released scanner compared to Ananthakrishnan et al. evaluating results from a prototype scanner with an earlier software version. Further, we focused our analysis on the liver, which allowed us a more detailed ROI placement to minimize any measuring bias: (i) carefully copying each ROI to the same location across reconstructions using screenshots for reference to maintain anatomical position despite respiratory motion and (ii) placing two ROI in each structure on different levels and averaging the results. This might also explain differences compared to Sauter et al. where only a single ROI for each structures was used.

Differences in VNC accuracy might also be explained by the different dual-energy CT systems available. For example, in SDCT acquisition data is accurately matched temporally and spatially due to the detector-based separation of photon energies. This allows for material decomposition in the projection domain which is not the case for all emission-based dual-energy solutions.^{3,12,25,26} Still, in a third-generation dual-source CT scanner, Durieux et al. showed high accuracies of VNC, *e.g.* mean differences between VNC and TNC of 0–2 HU for liver and spleen,²⁴ which were comparable to accuracies revealed in our study (*e.g.* mean attenuation differences of the liver: 0.1 ± 6.7 HU in CTA-abdomen). However, attenuation inaccuracies occurred in fluid, fat, and renal tissue; therefore, Durieux et al. concluded that VNC from the latest dual-source CT is not yet ready to completely replace TNC. Two studies investigating VNC in second-generation dual-source CT showed even higher differences between VNC and TNC acquisitions: one group reported differences of <10 HU in 75% of the $n = 86$ patients²³ while in another study with focus on the liver by Haji-Momeninan et al., reported mean attenuation differences of 5.4 ± 8.4 HU in $n = 48$ patients.⁸ So, the scanner generation and software version (*e.g.* applied algorithms) also appear to have a relevant impact on VNC performance.

Besides the accuracy of VNC to TNC images at a single time-point, also, the reproducibility of attenuation values in VNC in follow-up examinations needs to be considered. Recently, Obmann et al. showed that twin-beam and a second-generation dual-source dual-energy CT scanner differ in reproducibility of VNC attenuation.²⁷ The twin-beam dual-energy CT showed higher variations in VNC attenuation compared to the dual-source scanner. Further, the authors described that attenuation measurements in VNC cannot be reliably performed when different dual-energy approaches are used, so at this time point consistency of dual-energy scanner type in follow-up imaging is pivotal to generate reliable results.²⁷

Fatty liver disease is frequent in general population^{8,28} and holds relevant clinical implications,^{29,30} *e.g.* being a prognostic biomarker for cardiovascular events.³¹ Non-invasive, attenuation-based diagnosis of fatty liver disease with conventional CT gains more relevance^{8,28}; however, it historically requires unenhanced examinations.^{6–8} The aforementioned study from Haji-Momeninan et al. evaluated VNC for diagnosis of liver steatosis and reported promising results; however, accurate diagnosis was hampered by overestimation of attenuation in VNC of the liver and spleen. Smaller differences in attenuation between VNC and TNC as reported by Durieux et al. and in our study might therefore allow for improved diagnosis of liver steatosis^{3–5,24,32} but needs to be investigated in more pathology focused studies, as before reported overestimation of fat by VNC might negatively impact results.^{3,8,16} Eventually, this might allow screening for liver steatosis ‘on the fly’ in contrast-enhanced examinations in abdominal and cardiac imaging. In our cohort, iodine removal worked well not only for the whole liver but also in both liver lobes separately. This is an important finding as liver steatosis can occur asymmetrically and heterogeneously.^{6,8}

Following limitations need to be considered. A ROI-based evaluation of attenuation was used for evaluation of VNC accuracy, as it has been applied before.^{3,5,8,13,16} Nevertheless, a volumetric assessment of attenuation covering an entire organ or vessel might be less susceptible for any measuring bias. To minimize mismeasurement in our study, we used a pair of ROI on different levels of a standard size for each structure and averaged the results. Additionally, we tried to place the ROI in the same anatomical locations in each image set. Our study did not evaluate the performance of VNC for a certain pathology as there were not enough pathologies present; only 5 of 149 patients showed reduced liver attenuation indicating liver steatosis; however, we dedicated our analysis to the liver as a proof-of-concept for future clinical studies and pathology-based analysis. Still, in the few individual examples, as can be seen in Figure 4, VNC already showed its potential to be used for non-invasive attenuation-based diagnosis of liver steatosis. Another confounder that needs to be considered is that certain diseases, such as hemochromatosis, Wilson's and/or glycogen storage diseases as well as drug treatment with amiodarone can elevate liver attenuation and might affect VNC attenuation accuracies.³³

VNC from spectral-detector CT accurately removed iodine in a larger cohort of TAVR planning patients supporting analysis of liver attenuation in clinical routine. This could help to establish VNC as a substitute for TNC acquisition for liver evaluation. Care must be taken, however, not to rely on VNC images generated from tissue without contrast media present as they then may display false low attenuation values.

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