**Title:** Gadofosveset-enhanced thoracic venography: A comparative study evaluating steady state imaging versus conventional first-pass time-resolved dynamic imaging

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**Abstract**

**Background:** Dedicated blood-pool contrast agents combined with optimal angiographic protocols could improve the diagnostic accuracy of thoracic MR angiography.

**Purpose:** To assess the clinical utility of Gadofesveset-enhanced imaging and compare an optimized Steady State (SS) sequence against conventional first pass Dynamic Multi-Phase (DMP) imaging.

**Material and Methods:** Twenty-nine patients (17 male and 12 female, mean age 42.7, range 18-72 years) referred for MR thoracic venography were recruited. Imaging was performed on a 1.5T MRI system. A blood-pool contrast agent (Gadofesveset) was administered intravenously. Thirty temporal phases were acquired using DMP, this was immediately followed by a high resolution SS sequence. Three radiologists in consensus reviewed seven thoracic vascular segments after randomizing the acquisition order. Image quality, stenoses, thromboses and artifacts were graded using a categorical scoring system. The image quality for both approaches was compared using Wilcoxon’s signed-rank test. McNemar’s test was used to compare the proportions of stenosis grades, thrombus and artifacts.

**Results:** SS had significantly better image quality than DMP (3.14±0.73 and 2.92±0.60 respectively, p<0.001). SS identified less stenoses (>50%) than DMP, the differences in stenosis categorizations was statistically significant (p=0.013). There was no significant difference in the proportions of vessels with thromboses (p=0.617). DMP produced more artifacts than SS (101 vs 85), however, the difference was not statistically significant (p=0.073).

**Conclusion:** Gadofesveset-enhanced thoracic angiography is clinically feasible. SS imaging produces better image quality and fewer artifacts than conventional DMP imaging.

**Keywords:** Thoracic, Angiography, Contrast Agent, Steady State

**Clinical Trial Registration Details:** European Medicines Agency: EU Clinical Trials Registry. Trial Registration Number: 2007-002730-11, URL: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-002730-11/GB>.

**Introduction**

Establishing the patency of the central veins is an integral part of assessment of patients undergoing dialysis, parenteral nutrition, and where complex venous access is required, such as in multi-visceral transplantation. Repeated previous central venous catheter insertion and other venous interventions frequently lead to varying degrees of thrombo-occlusive disease and related stenoses (1). The role of imaging is to provide an accurate assessment of the site and extent of any venous disease and to identify possible etiologies in order to plan subsequent management and avoid related complications. Intravenous digital subtraction angiography (IV-DSA), color Doppler ultrasonography (CDUS) and computed tomography (CT) venography are commonly used, often in combination, for the evaluation of central venous patency.

MR imaging of the vascular system is increasingly utilized due to improved MR availability and the advantage of avoiding risks secondary to iodine based contrast media and ionizing radiation. Contrast-enhanced MR venography was first described in 1997 for lower extremity deep venous system evaluation (2), and MR venography of the upper extremity was later demonstrated with results consistent with conventional X-ray venography (3).

Dynamic high-spatial-resolution contrast-enhanced MR venography has been shown to be equally sensitive and specific for detecting stenoses and occlusions as conventional venography of the central veins of the chest (3-9). However, an intravenous injection of gadolinium-based contrast agent is required, and the majority of these conventional contrast agents are extracellular agents that rapidly leave the vascular compartment. The concentration difference between the veins and background tissues is often substantially reduced as these studies typically rely on peripheral arm vein injection of the contrast agent and subsequent circulation through the arterial and venous systems. Although adequate to characterize the general morphology and degree of stenosis, the signal available, and hence both spatial resolution and image quality of time-resolved images is often sub-optimal.

Over the past decade “long dwell” gadolinium based contrast agents have been developed that persist in the intravascular space due to reversible binding to albumin (10). Following injection and redistribution of contrast agents in the circulatory system vascular imaging can be performed during the equilibrium or “steady state” phase which typically lasts several hours. These techniques permit longer acquisition times as they are not limited by the first pass temporal limitations of conventional methods, and are particularly attractive for venous imaging as the contrast agent does not pass rapidly into the surrounding soft tissues.

The aim of this study was to evaluate and compare an optimized steady state (SS) sequence against a conventional first pass dynamic multi-phase (DMP) sequence using a blood pool contrast agent (gadofosveset trisodium) for evaluating the thoracic region in patients with suspected venous disease.

**Material and Methods**

This was a prospective open-label feasibility study which received clinical trial authorization (11). Ethics approval was obtained from the South-East Research Ethics Committee, UK (ethic application number: 07/H1102/109). Twenty-nine patients (17 male and 12 female, aged 42.7, range 18-72 years) routinely referred for MR angiography of the central veins were recruited. Exclusion criteria included contraindications to MRI (e.g. pacemaker, aneurysm clips, orbital metal), contraindications to intravenous gadolinium agents including patients with liver transplants and patients with impaired renal function with estimated Glomerular Filtration Rate <30 ml/min) and pregnant or lactating women. Informed written consent was obtained from each patient.

*MRI protocol*

All the examinations were performed using a 1.5T MRI system (Signa HDx, GE Healthcare, Waukesha, WI, USA) with an 8 channel cardiac receive array. Patients were placed in a supine position with their arms at their sides. After a three-plane localizer image was acquired, gadofosveset (ABLAVAR™: Lantheus Medical Imaging, North Billerica, MA, USA) was administered intravenously at a dose of 0.12ml/kg body weight (maximum 10ml) at 0.8ml/s, followed by a saline flush of 20ml at 2ml/s. The dynamic multi-phase sequence utilizes a temporal acceleration method referred to as TRICKS (time-resolved imaging of contrast kinetics) (12). The sequence was obtained in the coronal orientation 5 seconds after gadofosveset administration during shallow breathing, as per our standard acquisition. The optimized SS acquisition was performed immediately afterwards. The scan parameters are listed in Table 1. The entire examination took approximately 30 minutes.

*Image analysis*

The DMP and SS data sets were anonymized and reviewed on a PACS workstation (Centricity, GE Healthcare, Waukesha, WI, USA). The images were assessed in consensus by three consultant radiologists with 20 (DJL), 7 (TCS), and 2 (ES) years of experience in MRA reporting. The readers were allowed to individually adjust window centering and level settings of the MR data sets. The DMP and SS images were assessed independently and the order in which they were viewed was randomized to reduce recall bias. The readers were blinded to all clinical and demographic information. The DMP images were used as the reference standard for correct diagnosis. Seven venous segments were assessed in each patient: superior vena cava (SVC), left and right branches of brachiocephalic (LB, RB), subclavian (LS, RS) and the internal jugular (LI, RI).

On each examination and for each venous segment assessments were made of the following four areas:

i) Image quality in terms of vessel conspicuity using a four-point scale: excellent (optimal visualization of the vessel with no signal loss), good (slight signal loss but good overall visualization of the vessel), moderate (decreased signal intensity but images remain diagnostic) or poor (insufficient signal intensity such that the vessel is not completely identifiable and the image is not diagnostic).

ii) Presence of stenosis using a six-point scale: no stenosis (0% occlusion), mild (1-30%), mild-to-moderate (31-50%), moderate (51-75%), severe (76-99%), or total vessel occlusion. Each venous segment was evaluated for the highest degree of stenosis within that segment. Assessment of the degree of stenosis was not performed if a vessel could not be fully evaluated due to poor image quality.

iii) Presence of thrombosis: no thrombosis or partial/complete thrombosis. Assessment of the presence of thrombosis was not performed if a vessel could not be fully evaluated due to poor image quality.

iv) Presence of artifacts: none or mild/major artifacts impairing diagnosis.

*Statistical analysis*

The DMP and SS images were compared separately in terms of image quality; presence of stenosis; degree of thrombosis; and presence of artifacts. Normality assumptions were tested using the Shapiro-Wilk’s test. The image quality of both respective methods was compared using Wilcoxon’s signed-rank test. The specificity and sensitivity of the SS approach in detecting a stenosis >50% was performed relative to DMP. The specificity and sensitivity of the SS approach in detecting either a partial or complete thrombus was performed relative to DMP. McNemar’s test was performed to determine if the proportions of stenosis, thrombus and artifacts reported using SS were equivalent to DMP. A p-value <0.05 was defined as statistically significant. All the statistical analysis was performed using the R programming language (version 3.1.1, The R Foundation for Statistical Computing, Vienna, Austria).

**Results**

All 29 patients completed the DMP and SS examinations. No adverse events or reactions were reported following the administration of gadofosveset. A total 203 venous segments were assessed for both DMP and SS imaging (i.e. 7 vascular territories were analyzed in 29 separate patients).

*Image quality*

For SS and DMP the image quality from all venous segments was 3.14±0.73 [range 1-4], and 2.92±0.60 [range 2-4] respectively, the improvement in image quality using SS was statistically significant (p<0.001). A comparison of image quality in all vessels (Fig. 1a), illustrates that the SS technique had over twice as many vessel segments categorized as excellent when compared to DMP (67 vs 29). However, three vessel segments (2 in the left and 1 in the right subclavian) were categorized as having poor image quality using the SS technique and were subsequently excluded from stenosis classifications. A comparison of image quality for each vessel segment is shown in Table 2. The Table illustrates that the SS technique produced better image quality in each vessel segment and in two of the vessel segments the improvement was statistically significant (right branch of the brachiocephalic p=0.042, and right subclavian p=0.019).

*Stenosis categorizations*

The overall comparison of stenosis categorizations is shown in Table 3. The stenosis categorization comparing vessel segments with mild stenosis and above are shown graphically in Fig. 1b. The diagnostic utility of SS relative to DMP imaging in grading moderate stenosis and above was good (specificity 100%, sensitivity 91.9%). In total there were 8 vessels identified as >=50% stenosis using DMP which were subsequently graded as <50% using SS. Equivalence comparisons based on this criterion demonstrated the difference in stenosis characterization between techniques was statistically significant (McNemar’s *Χ2****=***6.125, p=0.013). An example of a discrepancy in stenosis characterization is illustrated in Fig. 2. In this instance the severe stenosis identified in the LS as classified using DMP appears to be a false positive as the SS images demonstrate vessel patency.

*Thrombus detection*

In total, using DMP imaging, 189 vessels were characterized as none, partial or complete thrombus, as 14 vessels were uninterpretable. Using SS, 191 vessels were characterized for thrombus as 12 vessels were uninterpretable. There was no significant difference in the proportions of thrombus detected (*Χ2=*0.25**,** p=0.617). SS has good specificity (81.3%) and sensitivity (99.5%) in detecting thrombus relative to DMP imaging. An example of thrombus detection is shown in Fig. 3. In this instance the steady state acquisition shows wall enhancement which in retrospect was also apparent on the last phase of the DMP acquisition.

*Artifacts*

The SS technique reported less artifacts than the conventional DMP approach, however, the difference was not statistically significant (*Χ2=*3.214,p=0.073). A representative example of mild artifacts that limit the ability for diagnosis using DMP is shown in Fig. 4. In this instance the additional SS acquisition facilitated diagnosis in all vessels except the SVC.

A representative example showing an instance when the DMP and SS images were equivalent is shown in Fig. 5. In this example the vessels were rated with good to excellent image quality and the artifacts were rated as none to mild.

**Discussion**

This study suggests that the SS approach produces overall better imaging quality and fewer artifacts than DMP imaging, this is encouraging as the longer scan time required for SS makes it more susceptible to motion. Our results also suggest that DMP and SS are in general consistent in detecting thrombus.

Gadofosveset owes its intravascular retention to a strong but reversible affinity to albumin, which extends the vascular lifetime of the contrast agent. As a result, lower doses are required, but this agent can still be used for the multiphase first pass imaging of blood vessels as it has similar relaxivity properties to conventional gadolinium agents. This occurs as gadofoveset is rapidly bound to albumin after injection producing similar T1 shortening as conventional gadolinium contrast agents residing in extracellular space.

Hadizadeh et al. previously reported on the utility of gadofosveset in peripheral angiography and compared SS and DMP against digital subtraction angiography as the gold standard (13). They found that the SS stenosis grades were more consistent with the gold standard DSA and that conventional DMP tended to overestimate stenosis grading. Our study also notes that DMP tends to overestimate the stenosis grade relative to SS. However, without DSA as a gold standard to reference it is impossible to infer which technique was most accurate.

The feasibility of a combined protocol for the MRI diagnosis of deep vein thrombosis and pulmonary embolism using gadofosveset trisodium has previously been reported (14). Its use for MRV of the leg veins and inferior vena cava using fat-suppressed 3D gradient echo Volume Interpolated Breath-hold Examination showedhigh diagnostic image quality with no cases of moderate, poor or non-diagnostic image quality. Additionally, an excellent inter-rater reliability was observed (15).

Although the SS-MRA offers all the advantages of a near isotropic 3D sequence, no information on flow dynamics can be obtained from the SS-MRA. Its use as a standalone technique is clinically adequate to assess central veins but a combination of DMP and SS techniques would complement each other and in our experience may avoid the need for conventional venography. The two different imaging sets allow for more detailed assessment of any ambiguous venous segments. Future studies of the central veins are warranted to formally assess if the combined protocol can improve diagnostic confidence and accuracy. Anzidei et al. reported on the assessment of carotid artery stenosis using gadofosveset-enhanced MR angiography and found that the steady-state image reading was superior to first-pass image reading, but noted that a combined reading proved most accurate (16).

The use of gadofosveset with SS imaging has also been found favorable in the assessment of other thoracic vasculature. In an analysis of 25 patients, ECG-gated, motion-compensated high-resolution SS-MRA of the thoracic vasculature (left superior pulmonary vein, left pulmonary artery and aortic arch) with gadofosveset offers significantly higher image quality and vessel sharpness when compared to standard first pass DMP MRA (17).

Separately, the development of non-contrast alternatives remains critical to address issues with Gadolinium agent administration, such as imaging patients with renal impairment. A notable study includes Tomasion et al. navigated SS approach to compensate for respiratory motion which reported good image quality metrics in the central veins in patients with vascular and cardiac disease (18). Further work in this area is warranted.

There are some limitations of our study. Consensus reading did not address individual variation in subjective assessment but this approach may enhance overall accuracy compared to independent single observers, thus leading to a maximum advantage of the techniques studied. Furthermore, use of consensus reading was deemed acceptable since the aim of this study was not to determine the general sensitivity and specificity of MR data sets, as compared with conventional venography data sets, but rather to elucidate the relative degree of diagnostic information obtained with DMP and SS images.

Conventional venography, which has its own limitations, has not been used as the reference standard as the clinical information obtained from MRV was considered sufficient and IV-DSA was not required in any of the cases following the MRV examinations. The average interpretation time was not evaluated in our study. However, it has been shown in other work that there was no significant increase in interpretation time when reading both data sets together compared with reading the high-spatial-resolution data set alone, despite the fact that there were more images overall to interpret (19).

In conclusion, we have found that MR venography with gadofosveset steady state imaging in the equilibrium phase produced significantly higher quality images with less artifacts than a conventional dynamic multi-phase time resolved technique, and was equivalent for the demonstration of venous stenosis and thrombosis.

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**Conflict of Interest Statement:** The Authors declare that they have no conflict of interest.

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**References**

1. Wilson SE. Vascular Access: Principals and Practice (5th Revised Edition). Philadelphia, PA: Lippincott Williams and Wilkins; 2009.

2. Lebowitz JA, Rofsky NM, Krinsky GA, et al. Gadolinium-enhanced body MR venography with subtraction technique. Am J Roentgenol 1997;169:755-758.

3. Kroencke TJ, Taupitz M, Arnold R, et al. Three-dimensional gadolinium-enhanced magnetic resonance venography in suspected thrombo-occlusive disease of the central chest veins. Chest 2001;120:1570-1576.

4. Shinde TS, Lee VS, Rofsky NM, et al. Three-dimensional gadolinium-enhanced MR venographic evaluation of patency of central veins in the thorax: initial experience. Radiology 1999;213:555-560.

5. Nael K, Laub G, Finn JP. Three-dimensional contrast-enhanced MR angiography of the thoraco-abdominal vessels. Magn Reson Imaging Clin N Am 2005;13:359-380.

6. Thornton MJ, Ryan R, Varghese JC, et al. A three-dimensional gadolinium-enhanced MR venography technique for imaging central veins. Am J Roentgenol 1999;173:999-1003.

7. Tanju S, Sancak T, Dusunceli E, et al. Direct contrast-enhanced 3D MR venography evaluation of upper extremity deep venous system. Diagn Interv Radiol 2006;12:74-79.

8. Oxtoby JW, Widjaja E, Gibson KM, et al. 3D gadolinium-enhanced MRI venography: evaluation of central chest veins and impact on patient management. Clin Radiol 2001;56:887-894.

9. Fraser DG, Moody AR, Davidson IR, et al. Deep venous thrombosis: diagnosis by using venous enhanced subtracted peak arterial MR venography versus conventional venography. Radiology 2003;226:812-820.

10. Goyen M. Gadofosveset-enhanced magnetic resonance angiography. Vasc Health Risk Manag 2008;4:1-9.

11. European Medicines Agency: EU Clinical Trials Registry [Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-002730-11/GB.]

12. Korosec FR, Frayne R, Grist TM, et al. Time-resolved contrast-enhanced 3D MR angiography. Magn Reson Med 1996;36:345-351.

13. Hadizadeh DR, Gieseke J, Lohmaier SH, et al. Peripheral MR angiography with blood pool contrast agent: prospective intraindividual comparative study of high-spatial-resolution steady-state MR angiography versus standard-resolution first-pass MR angiography and DSA. Radiology 2008;249:701-711.

14. Hansch A, Betge S, Poehlmann G, et al. Combined magnetic resonance imaging of deep venous thrombosis and pulmonary arteries after a single injection of a blood pool contrast agent. Eur Radiol 2011;21:318-325.

15. Pfeil A, Betge S, Poehlmann G, et al. Magnetic resonance VIBE venography using the blood pool contrast agent gadofosveset trisodium--an interrater reliability study. Eur J Radiol 2012;81:547-552.

16. Anzidei M, Napoli A, Marincola BC, et al. Gadofosveset-enhanced MR angiography of carotid arteries: does steady-state imaging improve accuracy of first-pass imaging? Comparison with selective digital subtraction angiography. Radiology 2009;251:457-466.

17. Naehle CP, Muller A, Willinek WA, et al. First-pass and steady-state magnetic resonance angiography of the thoracic vasculature using gadofosveset trisodium. J Magn Reson Imaging 2009;30:809-816.

18. Tomasian A, Lohan DG, Laub G, Singhal A, Finn JP, Krishnam MS. Noncontrast 3D steady state free precession magnetic resonance angiography of the thoracic central veins using nonselective radiofrequency excitation over a large field of view: initial experience. Invest Radiology 2008;43:306-313

19. Kim CY, Mirza RA, Bryant JA, et al. Central veins of the chest: evaluation with time-resolved MR angiography. Radiology 2008;247:558-566.

**Table 1 Pulse sequence parameters**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  | **DMP** |  | **SS** | |
|  |  |  |  | |
|  |  |  |  | |
| ***k*-space acquisition** | 3D |  | 3D | |
| **Sequence** | Fast SPGR§ |  | Fast SPGR | |
| **TE/TR (ms)** | 1.8/4.6 |  | 2/5.4 | |
| **Flip Angle** | 30º |  | 30º | |
| **Matrix Size (Acq)** | 418×256 |  | 512×512 | |
| **Matrix Size (Recon)** | 512×512 |  | 1024×1024 | |
| **NEX** | 0.75 |  | 2 | |
| **ASSET factor** | 2 (phase) |  | NA | |
| **FOV (cm)** | 40×40 |  | 40×40 | |
| **No. of Slices** | 42 |  | 64 | |
| **Slice Thickness (mm)** | 2.6\* |  | 1.6\* | |
| **No. of Phases** | 30 |  | 1 | |
| **Acq Time (min:sec)** | 3:26 |  | 4:26 | |
|  |  |  |  |  |

§ The DMP acquisition employs TRICKS temporal acceleration

\*slice thickness is reconstructed to 1.3mm and 0.8mm for DMP and SS respectively

**Table 2** **Comparison of image quality using DMP and SS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **(n)** | **TRICKS** | **SS** | **p-value** |
| SVC | 29 | 2.55±0.51 | 2.62±0.56 | 0.565 |
| RB | 29 | 2.93±0.53 | 3.24±0.64 | 0.042\* |
| RS | 29 | 2.93±0.59 | 3.31±0.85 | 0.019\* |
| RI | 29 | 3.10±0.67 | 3.28±0.65 | 0.220 |
| LB | 29 | 2.76±0.64 | 3.00±0.65 | 0.107 |
| LS | 29 | 3.07±0.53 | 3.24±0.87 | 0.144 |
| LI | 29 | 3.10±0.56 | 3.28±0.65 | 0.212 |

mean±stdev

\* statistically significant (p<0.05)

**Table 3** **Comparison of stenosis categorizations using DMP and SS.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Stenosis** | **DMP** | **SS** |
|  |  | n=203 | n=200 |
| None | 0% | 125 | 135 |
| Mild | 1-30% | 5 | 4 |
| Mild/Moderate | 31-50% | 6 | 4 |
| Moderate | 51-75% | 6 | 3 |
| Severe | 75-99% | 13 | 14 |
| Total | 100% | 48 | 40 |

n = number of interpretable images for stenosis grading.

**Figures**

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Fig. 1. (a) Image quality categorizations incorporating all 203 vessel segments, and (b) stenosis categorizations for mild stenosis and above (DMP (red) and SS (green))

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Fig. 2. A discrepancy in stenosis characterization was noted between techniques in several patients. This example, of a 31-year-old female, illustrates a probable false positive characterization whereby DMP (a) identified a severe stenosis within the left subclavian vein whereas the corresponding SS images (b) identified a patent vessel proximal to a valve.

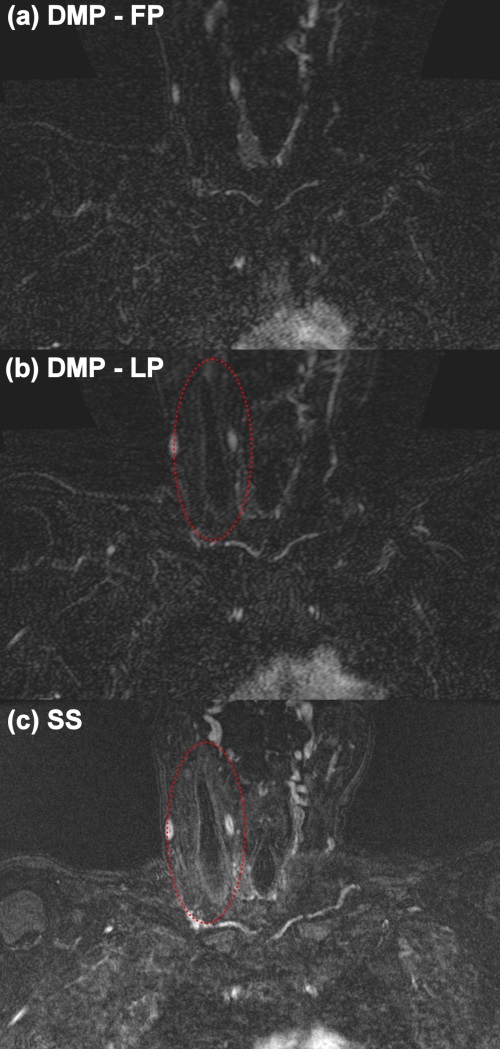


Fig. 3. A discrepancy in thrombus characterization, on a 56-year-old female, in the right internal jugular vein. The blind review of the initial first pass of DMP (a) defined the internal jugular as not assessable. The review of the SS images (c) identified a large thrombus with wall enhancement in the internal jugular. Subsequent retrospective analysis of the DMP dataset noted less obvious wall enhancement in the last phase (LP) of the DMP acquisition (b)

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Fig. 4. A 32-year-old male patient in which the DMP images (a) present moderate to good image quality but demonstrate mild artifacts across most vessels (SVC, RB, RS, LB, LS, LI). The corresponding SS images (b) were rated good to excellent with mild artifacts present involving the SVC

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Fig. 5. A 56-year-old male patient in which the DMP (a & b) and SS (c) images were rated with equivalent image quality (characterized as good to excellent). The presence of artifacts were also equivalent (rated as none to mild). Note: the patient has a catheter in situ (transiting the right subclavian and the right brachiocephalic vein).