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R. Bammer and S.A. Amukotuwa



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# Navigating Supply Chain Disruptions of Iodinated Contrast Agent for Neuroimaging and How Business Intelligence Can Help the Decision Process

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## ABSTRACT

**SUMMARY:** A recent coronavirus disease 2019–related shutdown of the main production facility of iohexol in China has led to massive shortages of iodinated contrast material across the globe. This shortage has also jeopardized neuroimaging. In this article, we describe remedies to reduce iodinated contrast material use for stroke imaging, which is its primary use in neuroimaging, that we have implemented in our hospital network.


**ABBREVIATIONS:** BI = Business Intelligence; CE = contrast-enhanced; coronavirus disease = COVID; ECR = endovascular clot retrieval; ICM = iodinated contrast material; Tmax = time-to-maximum

The latest knock-on effect of the coronavirus disease 2019 (COVID-19) pandemic is a global shortage of iodinated contrast medium (ICM) triggered by the shutdown of GE Healthcare's main production facility of iohexol (Omnipaque; GE Healthcare) during the latest lockdown in Shanghai at the end of March 2022. The combination of the company's Just-in-Time inventory management and lean production strategies that afforded competitive pricing (~$0.13/mL for our institution) and GE's large global market share of ICM has led to a massive disruption in the global supply of ICM, which caught many of us by surprise. With stock levels dwindling and unclear information on when the factory will return to full capacity or make up for the production shortfall, many hospitals are scrambling to source more ICM from elsewhere. This unusual sudden demand, in turn, leads to an additional squeeze on the ICM supply chain. Several professional interest groups, including the American College of Radiology[1] and the American Society of Hospital Pharmacists,[2] have issued guidance documents on how to address the current ICM shortage, including various strategies for conservation of contrast material for those diagnostic tests and interventions that are time-critical and without which patients would die or have considerable morbidity. A recent clinical perspective in the *American Journal of Roentgenology* highlighted several broad strategies to conserve ICM at imaging facilities.[3] This perspective focusses on the most frequent indication for contrast-enhanced (CE) CT in neuroimaging: Code Stroke.

### *Overcoming the ICM Shortage*

Here, we report the status quo and ICM shortage remedies implemented on May 13, 2022, at our institution and provide guidance on imaging protocol changes. A bottom-up analysis using our own Business Intelligence (BI) tools showed that the minimum contrast usage after the intervention could be as low as 10% of our precrisis ICM usage. We hope that some of the insights from our intervention can also be of use to others in the neuroradiology community.

Our institution is the largest public hospital network in Australia and comprises a tertiary referral center, which is also a comprehensive stroke center, 2 large peripheral metropolitan hubs, and an oncology center, all located in the southeastern metropolitan area of Melbourne. Our estimated catchment is approximately 2.75 million people. Across our network, our annual expenditure on CT contrast agents is $465,000. We use approximately 15.9 L of ICM per day, of which 15 L is Omnipaque; the remainder is iodixanol (Visipaque; GE Healthcare), which is primarily used in the catheterization laboratory.

Evidence from our department's BI tools shows that before the ICM shortage, cardiac, chest, and abdominal CT imaging accounted for ~70% of all contrast agent usage, while Code Stroke accounted for 10% and was, therefore, by far the largest user of ICM in the diagnostic (noninterventional) neuroimaging category (Fig 1). If available at other institutions, we recommend that readers use similar BI tools to analyze the case mix at their institutions because it might differ from ours. A breakdown of the biggest ICM users via BI tools can be helpful in assessing

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From Monash Imaging, Monash Health, Clayton, Victoria, Australia; and Department of Radiology, Monash University, Clayton, Victoria, Australia.

Please address correspondence to Roland Bammer, MBA, PhD, Department of Radiology, Monash University, Monash Medical Centre, 246 Clayton Rd, Clayton, VIC 3168, Australia; e-mail: roland.bammer@monash.edu



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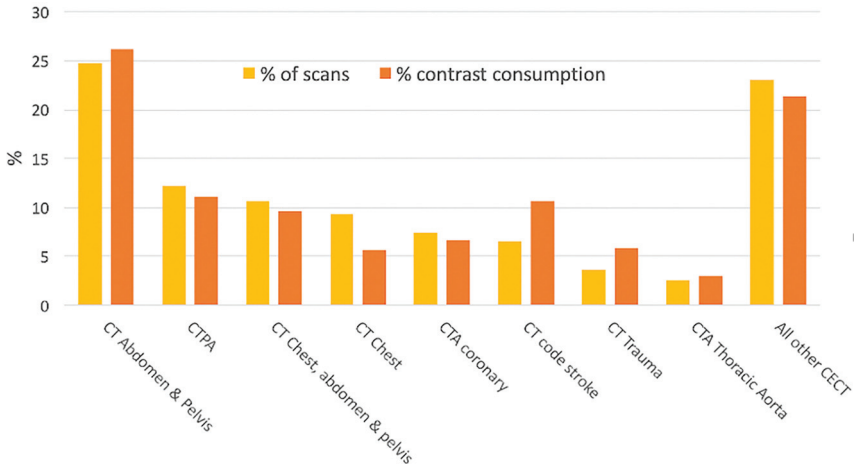


**FIG 1.** The most common use of an iodinated contrast agent in CT imaging (CT PA indicates CT pulmonary angiography).

which sectors are the most frequent users of contrast agent and are, therefore, most likely to yield significant reduction of ICM usage if targeted with ICM-reducing interventions.

As of May 16, 2022, our current inventory would have lasted for another 2.5 weeks based on our normal operational ICM consumption rate (note some Australian hospitals have already exhausted their supply and depend on support from the Department of Health and other hospitals). We, therefore, urgently needed strategies to conserve ICM.

The ICM shortage remedies that we implemented fall into 5 major categories:

1) Mandate "CT with contrast" ordered by an attending physician or specialist advanced trainee and have a communication plan for referring physicians to employ appropriate use criteria for contrast-based CT examinations.
2) Modify protocols to scan without contrast agent.
3) Use alternative imaging modalities in lieu of CE CT.
4) Optimize CT scan protocols to use less ICM.
5) Prioritize inpatient imaging over outpatient studies.

The order in which the 5 categories are implemented depends on the organ systems imaged. For example, at our institution, applying category 2 (ie, switching to unenhanced CTs for chest, abdomen, and pelvis studies) was one of the easiest and most effective measures to implement in body radiology, yielding a substantial reduction ICM usage.

For diagnostic neuroimaging, the other 4 categories were the preferred interventions, which we will discuss in more detail next. Code Stroke is the primary user of ICM in diagnostic neuroradiology, accounting for approximately 60% of all ICM use in neuroradiology CTs (71% if only emergent studies are considered). Evidence from our BI tools also showed the use (from most-to-least volume use in diagnostic neuroimaging) of ICM for CTA for SAH and parenchymal hematoma to identify aneurysms and vascular malformations (10%); CTA for identifying carotid disease (9%); CE CT of the brain (7%); and CE CT imaging of the neck (5.5%); but the volumes were, even in aggregate, much less than our institution's use for Code Stroke. Hence, the remainder of this document will focus solely on Code Stroke.

**Category 1: Mandate CE CTs Ordered by Attending Referring Stroke Neurology Physicians Only.** Within the past 12 months, we have observed a considerable increase (40%) in orders for Code Stroke multimodal (head CT, CTA of head and neck, and CTP) studies from our emergency and stroke services across the network. Aside from a general increase of Code Stroke CTs performed globally due to the broad adoption of endovascular clot retrieval (ECR),[4] at our institution, this increase has also aligned with implementation of ordering imaging studies directly via our electronic medical records and overcrowding of our emergency departments.[5] Facilitated by the ease of electronic medical record–based ordering, we have noticed that junior doctors have a lower threshold for ordering multimodal CT scans than more senior clinicians. Our emergency departments have an overreliance on imaging for ruling out strokes to facilitate patient discharge.

In the first 48 hours since we mandated that imaging tests need to be ordered by an attending stroke neurologist, the number of multimodal CTs was reduced to 43% of the average daily volume ordered in the 12 weeks before our intervention. Most interesting, the ratio of positive findings to the number Code Stroke CT scans ordered increased to 25%, which is in stark contrast to the 8% rate during the 12 weeks prior.

**Category 2: Modify Scanning Protocols to Scan without Contrast Agent.** It is well-known that the diagnostic sensitivity and specificity of unenhanced CT is relatively poor, particularly in the hyperacute phase of a stroke.[6] Specific indications such as sulcal effacement, the insular ribbon sign, and loss of gray/white contrast are more apparent in established infarcts, while the hyperdense vessel sign strongly depends on clot composition. Assessing the true size of the irreversibly damaged tissue can also be fraught with poor sensitivity and variability due to poor contrast and reader subjectivity. Even when augmented by artificial intelligence, eg, artificial intelligence–driven ASPECTS,[7] identifying the site of occlusion or assessing how much salvageable tissue remains is often not possible without perfusion or angiographic imaging. Generally, ASPECTS is useful to rule out patients receiving ECR, but unenhanced CT and ASPECTS are not well-suited to rule in patients. Moreover, angiographic assessment of the neck and intracranial vessels is still needed to establish the presence of large-vessel occlusion. The risk of patients missing out on potentially beneficial treatment is too high. Therefore, we cannot advocate foregoing the use of ICM in the acute stroke work-up. If CT is the technique to use for a Code Stroke, we still perform multimodal CT albeit with a lesser amount of ICM. For even more conservative approaches, an unenhanced CT (with ASPECTS) can be augmented by a CTA, preferably with a reduced ICM injection volume.

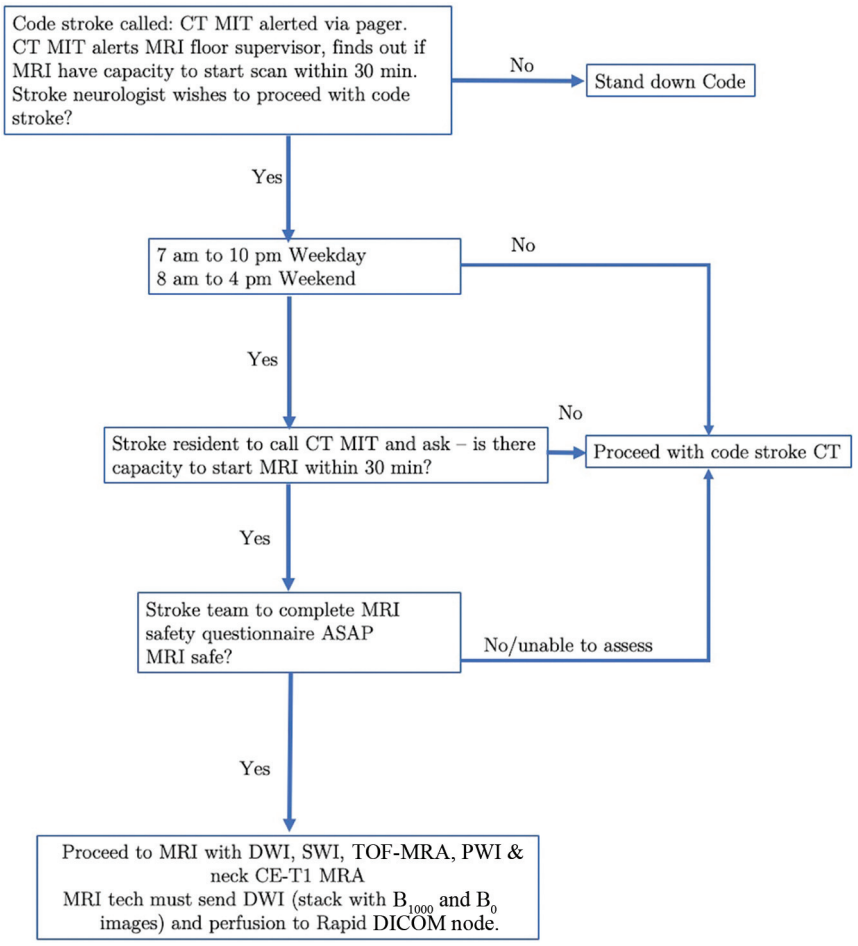


**FIG 2.** MR imaging/CT decision tree for Code Stroke. ASAP indicates as soon as possible.

**Category 3: Use Alternative Imaging Modalities in Lieu of CE CT.** DWI has exquisite diagnostic sensitivity for detecting acute stroke lesions and is considered the definitive test.[6] Gradient-echo or susceptibility-weighted imaging as well as FLAIR or even $b_0$ DWI and prebolus DSC-PWI allow one to detect hemorrhage with sensitivities that are comparable with or superior to CT.[8-10] Moreover, DSC-PWI is equally well established to determine tissue-at-risk as CTP.

Two shortcomings of MR imaging use are the typical MR imaging contraindications (eg, pacemakers and stimulators, aneurysm clips, and so forth) and 24/7 availability. In addition, inpatient MRIs are frequently used for other complex examinations, making access logistically more challenging. Moreover, MR imaging is considered a rather lengthy examination, typically lasting 20–30 minutes, whereas the door-to-CT time at our institution is ≤10 minutes and the duration of the multimodal CT is around 5 minutes.

In response to the ICM shortage, we have worked with our entire stroke care and MR imaging team to implement an acute stroke (fast) MR imaging protocol and workflow, which we have tested successfully, to achieve short door-to-MRI scan turnaround times, but our goal was to reduce ICM usage and not to fully replace multimodal CT. Our default is still multimodal CT, for example after-hours when our MRIs are not staffed with on-site personnel, when patients' contraindications to MR imaging cannot be safely excluded either by reviewing screening forms with the patient or next of kin or via a fast mobile x-ray, or when the patient is unlikely to fit into the scanner bore (>120 kg). The decision flow chart under which our team is operating is shown in Fig 2. Because stroke is a time-critical emergency and delay to treatment must be avoided, this workflow factors in how quickly a slot in one of our MRIs can be made available. For example, if a lengthy scan on a complex ICU patient, a patient with a conditional pacemaker, or a patient with cord compression is underway on our inpatient MR imaging scanners, the patient is automatically diverted to CT.

The primary purpose of sending patients to urgent stroke MR imaging is to identify patients with large-vessel occlusion who qualify for ECR. On the basis of the experience of the authors who have designed the CT and MR imaging protocols for several clinical trials,[11-13] we have set up 5-minute acute stroke MR imaging protocols akin to the protocols used in Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE 3).[14] These minimalistic protocols are tailored to determine the following: 1) infarct core (DWI); 2) the presence of hemorrhage (SWI); 3) large-vessel occlusion (3D TOF-MRA); 4) at-risk tissue (time-to-maximum [Tmax] from DSC-PWI); and 5) proximal occlusion (CE T1WI MRA). They are tuned for speed and not for resolution yet provide sufficient quality for stroke diagnosis. We also use the residual equilibrium contrast agent circulating through the blood stream immediately after the DSC-PWI instead of using a second bolus injection for the CE MRA, which is sufficient to visualize the large neck vessels and saves time. Specifically, we use a 1- minute axial 3D Dixon volumetric interpolated breath-hold examination (DIXON VIBE) sequence with 2-mm section resolution covering the arch to skull base. Alternatively, the single bolus can be divided into DSC-PWI and CE MRA if the overall use of gadolinium-based contrast agent is a concern.

Most current MR imaging systems have parallel imaging and other acceleration techniques available. To achieve stroke protocols in <5 minutes still requires accepting lower resolution and thicker slices and perhaps a bit more distortion on the EPI scans than found on the longer protocols. Figure 3 shows typical results for a fast (Avanto 1.5T; Siemens) MR imaging protocol. An example of an MR imaging protocol (3T Verio; Siemens) can be found in the Online Supplemental Data. The key to successful implementation is to understand that the role of MR imaging in the acute setting is to find ECR candidates with salvageable tissue and to rule out brain

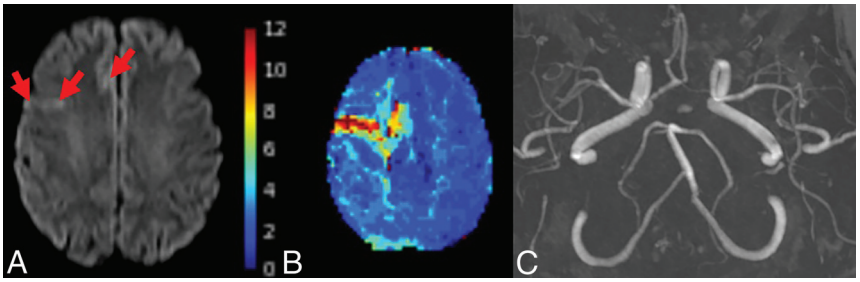


**FIG 3.** Acute fast Code Stroke MR imaging. A 51-year-old woman with new left-sided weakness, last seen well 12 hours earlier. Abbreviated MR imaging protocol with fast DWI, PWI, SWI, TOF-MRA, and T1 neck was performed. *A*, DWI shows small foci of cortical restricted diffusion in the right frontal lobe in the MCA and anterior cerebral artery territories. *B*, The Tmax map shows severe delay in the distribution of the right MCA M3 and anterior cerebral artery A4 branches. *C*, TOF-MRA MIP shows no large-vessel occlusion. An M3 occlusion is evident on source images.

hemorrhage. Most embolic infarcts can also be depicted on a 30- to 40-second DWI, and the PWI allows detection of mid-to-distal vessel occlusions using Tmax maps.[15] In fact, small emboli and distal vessel occlusions are often not detected on CT and CTA, though CTP has helped to increase diagnostic sensitivity.[16,17] Patients who do not have a stroke but have imaging findings suggestive of an alternative pathology can undergo a more comprehensive MR imaging examination later if further sequences or better spatial resolution is required for diagnosis.

We had not previously used MR imaging as the first-line technique for Code Stroke and have encountered some initial issues in overcoming the logistic challenges in an already-busy inpatient MR imaging service. If MR imaging is not a part of your institution's usual Code Stroke process, it is vital to have a clear communication plan to ensure short door-to-scanner and door-to-needle times when implementing this change. This includes clear instructions to the stroke and emergency department teams, such as when to send patients to MR imaging and not to CT and which new phone numbers and pagers to call. The neuroradiologist acts as a change manager and fulfills a crucial role in motivating an MR imaging team to embrace this new challenge.

Category 4: Optimize CT Scan Protocols to Use Less ICM. There are different vectors along which scan protocols can be altered to reduce ICM usage. Next, we will discuss those interventions that we have instituted in our network.

1) Shift multimodal stroke imaging to wide-detector CTs (when available). We shifted most of our patients with Code Stroke to our 320-detector-row CT (Aquilion One; Toshiba) scanner and set up a straightforward "burst mode" CTP protocol with 140-mm z-coverage. This change allows whole-brain CTA to be reconstructed from the CTP. Five seconds into the CTP scan, we acquired a bone mask at a higher SNR for subtraction (310 mA, 0.75-second rotation time, 80 kV[peak]), which was followed by a dynamic scan (29 cycles, 2-second cycle time, 150 mA, 0.75-second rotation time, 80 kVp) that started 10 seconds after the bolus injection. We used only 40 mL of Omnipaque at a flow rate of 6 mL/sec followed by a 60-mL saline chaser at the same flow rate. This acquisition allows us to compute all perfusion parameter maps (eg, CBF and Tmax) relevant for mismatch analysis. While the time series data were sent off to compute the perfusion parameter maps, we identified the timeframe with the peak arterial concentration at the ipsilateral side, and using 0.5- or 1.0-mm slice collimation allowed us to also reconstruct an intracranial angiogram from this CTP timeframe. A sample CTP protocol can be found in the Online Supplemental Data.

Immediately following the CTP, while iodine was still recirculating, a CT from the aortic arch to circle of Willis was performed that was topped up with another 20- to 40-mL iodine bolus to visualize the neck vessel, to rule out any proximal occlusions, and assess arterial access; we found the venous overlay acceptable. To boost the CTA contrast, we reduced the tube voltage of our standard head and neck CTA to 80 kVp. Figure 4 shows an example of such a scan. Alternatively, Oei et al[18,19] implemented an interleaved CTP and arch to the circle of Willis CTA approach on the Toshiba 320. At the peak arterial concentration, the CTP was interrupted for 4 seconds to allow an arch to the circle of Willis CTA, after which the table was returned and the CTP was completed. We have not implemented the Oei approach mainly because it requires manual triggering of the CTA and is difficult to protocol, which is a concern when we must train a large CT technologist workforce.

2) We have also adjusted our other protocols (eg, Discovery CT750 HD GSI; GE Healthcare), similar to our wide-detector CTs. First, we have reduced the injected iodine for CTP from 60 to 40 mL. Note that all our CTP protocols were already at the lowest setting (70 or 80 kVp) to get closest to the K-edge of iodine. Second, similar to the wide detector protocol above (1), we performed CTA immediately after CTP to use residual contrast. Third, we reduced our CTA iodine injection volume from 70 to 30–40 mL and lowered the tube voltage settings of our standard CTA to 80 kVp (Fig 5). An example the CTP protocol can be found in the Online Supplemental Data. Because the injected volume for the CTA is smaller, we have noticed that some of the iodine may be held up in upper limb and axillary veins and is not fully pushed into the central circulation. We, therefore, advise using a large volume of saline chaser (eg, 60mL) to ensure that all the ICM is safely pushed out of the injector tubing and arm veins into the central circulation.

The compactness of the bolus usually also depends on the injection flow rate. With smaller injection volumes, it is, therefore, good to use higher flow rates. Some dispersion will occur in any case when passing through the lung circulation. Nevertheless, a sharper bolus means more iodine per unit of blood volume and thus more attenuation. Due to the shorter bolus, the triggering of the CTA requires proper fluoro triggering because the CTA will be more sensitive to incorrect timing. Lowering the trigger threshold by 15%–20% can avoid missing the bolus. For taller patients, a larger (40–50mL) bolus will still be needed. Here, the blood volume in which the iodine is distributed in the central circulation depends not only on the patient's weight but also his or her height,

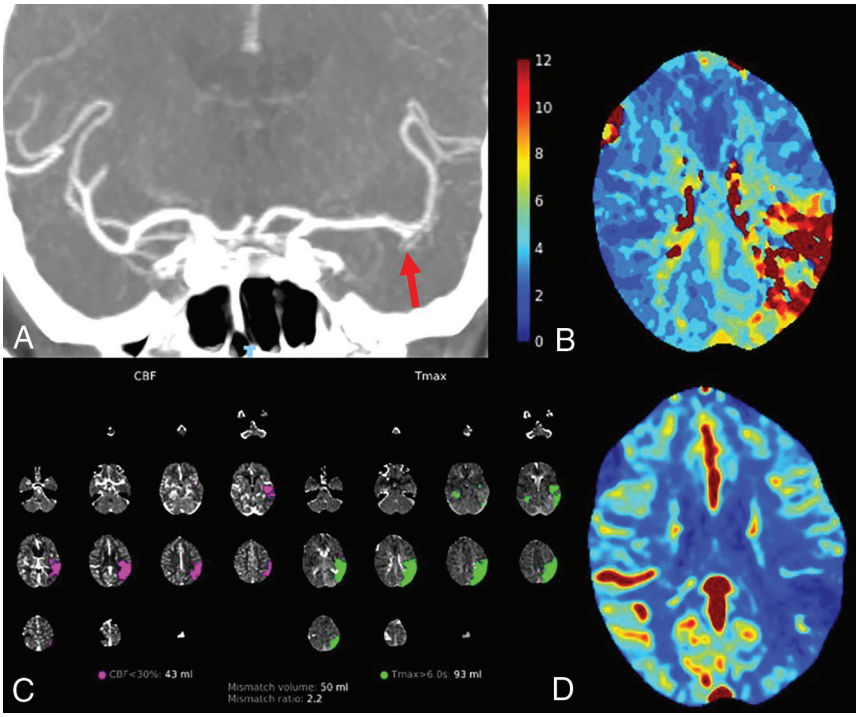


**FIG 4.** Sample of 40-mL CTP/CTA obtained on a Toshiba 320 scanner. Images from a 79-year-old woman who presented with sudden-onset expressive dysphasia. *A*, MIP CTA images reconstructed from the CTP acquisition at peak arterial opacification demonstrate good opacification of medium and distal intracranial arteries. Proximal occlusion of the left MCA inferior to the M2 division (*arrow*) is evident. *B* and *D*, Selected slices of Tmax and relative CBF maps show marked territorial Tmax delay and reduced rCBF. The subarachnoid space over the right frontal lobe is focally dilated. *C*, CTP, relative CBF, and Tmax mismatch maps show that there is some salvageable penumbra. Diagnostic-quality CTP was maintained despite contrast dose reduction.

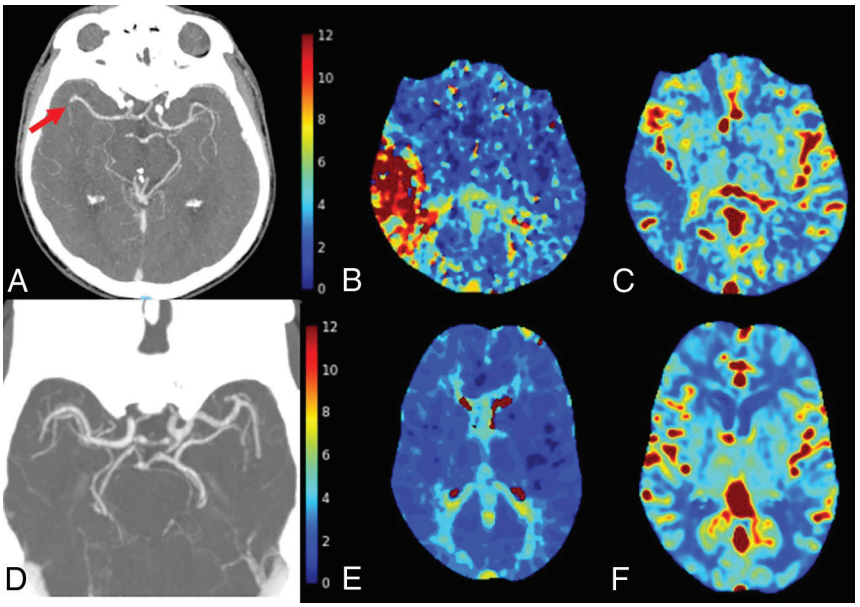


**FIG 5.** Examples of 20-mL CTA performed on small-detector-width CT (Discovery 750; GE Healthcare). *A*, Axial CTA MIP demonstrates occlusion of the inferior M2 division of the right MCA (*arrow*) in a 75-year-old man with sudden-onset abnormal left-sided movements. *B* and *C*, A single section of Tmax and rCBF maps shows territorial Tmax delay and a small area of severely reduced relative CBF. *D*, Sample of an axial CTA MIP in a different patient, a 71-year-old woman with right-sided weakness. The patient had a low weight (50 kg), accounting for the superior arterial opacification with the same contrast load. *E* and *F*, Selected Tmax and relative CBF images show that the CTP quality is excellent.

connected through the body mass index. For a more optimized weight-based volume calculation, especially in patients with obesity, the interested reader is directed to the Lemmens-Bernstein-Brodsky formula.[20] Reviewing the time density curve from the preceding CTP study, mainly the time of arrival and the width of the arterial input function (eg, >20 seconds), also helps to identify patients with poor cardiac output or ejection fraction, another factor that sometimes impacts CTAs. In our experience, roughly 20% of patients with Code Stroke present with poor cardiac output. For such patients, it is also prudent to use at least 40 mL of ICM to ensure sufficient vessel opacification.

Dual-energy CT scanning also allows acquiring images at a lower kilovolt(peak) and thus bringing the acquisition closer to the K-edge of iodine. Consequently, less iodine is needed to create comparable vascular contrast than at high kilovolt(peak) settings. We are cognizant, however, that dual-energy CT scanners are less prevalent in the global installation base of CT scanners and are largely limited to academic centers and referral centers. While we have implemented dual-energy scanning on our body CT protocols, we have not done so for neuroimaging protocols.

At our institution, we have decided against foregoing CTP and just relying on an unenhanced CT and CTA because CTP provides important diagnostic information beyond large-vessel occlusions. We have shown that distal vessel occlusions and other diseases causing hemodynamic abnormalities can be detected much faster and with greater confidence than on CTA alone.[16,17] This added diagnostic capability is critical to our clinical referrers, who rely on it to guide decisions on distal vessel thrombectomy, thrombolysis beyond 4.5 hours, and patient discharge instead of admission for further work-up if CTP findings are normal. We think that after reducing the ICM of our multimodal CT Code Stroke protocol from 130 to 60 mL; directing Code Stroke in-hours to MR imaging; and having attendings instead of trainees requesting CE studies, our ICM for CTP studies can be well-justified in the interest

of patient care. Before the ICM shortage, our daily contrast usage for Code Stroke work-up was approximately 1.0 L per day. In the 96 hours since all the aforementioned interventions were implemented, the new daily ICM consumption for Code Stroke work-up has been 0.12 L (88% reduction). The average number of Code Stroke CTs decreased from 8 per day to 2 per day. Overall, ICM consumption for all CT studies was reduced by 72% in our network within the same period. At this time, we have no evidence that we have missed strokes that were later seen with DWI.

Category 5: Prioritize Inpatient and Emergency Imaging over Outpatient Studies. Patients with Code Stroke present at our institutions through the emergency department or stroke service as inpatients and receive priority. Deferment of imaging is not an option for patients with acute ischemic stroke who are at high risk of death and significant morbidity without treatment. For transient symptoms, work-up within 48 hours of presentation is recommended by the American Heart Association/American Stroke Association guidelines.[21] We will continue to offer these patients urgent outpatient brain MRIs but replace CTA with carotid sonography within 48 hours to conserve ICM.

The other emergent, time-critical ICM-consuming neuroimaging study for which CT is preferred over MR imaging because of access is brain CTA for SAH. We will divert these to MR imaging with TOF-MRA when our ICM supplies become critically low. Most diagnostic neuroradiology work-up is via MR imaging, and when reviewing our BI data, we found negligible use of ICM for our outpatient work.

Of course, the implementation of protocol and workflow changes requires buy-in from all health care professionals involved in the patient experience. In our opinion, it is of paramount importance to have a proper change-management process in place that involves all stakeholders. Due to the relatively sudden onset of the crisis and several of the implemented changes being quite substantial and demanding for some staff, we cannot emphasize enough how important it is to have frequent and clear communication of changes and "champions" identified when trying to establish these alterations. Moreover, if you lead the change process, it is also critical to ensure that the changes are adequately followed through and risks are properly anticipated, identified, and managed.

The silver lining is that this crisis has shown us that for many examinations, we can get by with substantially less contrast material without sacrificing diagnostic capability. It has also highlighted the role and value of alternative tests. This begs the question: Why have these approaches not been used earlier? After all, significant annual costs are associated with current ICM volumes. Nevertheless, it cannot be assumed that there will be an overall cost-savings from this period of reduced ICM usage. This is a multifaceted problem. Many tests will be moved to MR imaging, for which the contrast agent is more expensive, and there are opportunity costs when either displacing other patients or stretching MR imaging capacity to accommodate more patients. It also needs to be shown how these new measures will affect diagnostic accuracy as well as their overall effect on patient and health economics outcomes.


### *Summary*

The supply chain disruptions of ICM due to COVID-19 lockdowns in March 2022 in China caught most of us by surprise. A few larger customers were forewarned by the vendor and could replenish their supplies in time, but most hospitals were caught off guard. With this Practice Perspectives, we wanted to share with the *American Journal of Neuroradiology* readership the measures that our institution has put in place to weather this shortage. In such unprecedented times, we wanted to lend our experience from protocolling many stroke studies to the broader community. We are cognizant that there are multiple ways to reduce ICM and ours is just one of many versions.* An interesting question arises from this ICM crisis and the forced ICM austerity measures: Will we ever return to the large volumes of ICM use? Maybe this reset was long overdue. Many of the CTA protocols, for example, were grandfathered in from times when CT scanners were slower and the bolus outran the table movements. Times have change, and if start of CTA acquisition timed correctly, a narrow, less voluminous bolus can be easily chased by a modern scanner.



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*MR imaging and CT scan protocols can vary between make and models. Interested readers can contact the authors for specific protocols. A few sample protocols can be found in the Online Supplemental Data.

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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