Received: 20 June 2024 | Accepted: 31 July 2024
DOI: 10.1002/agm2.12345

Aging Medicine Open Access WILEY

CONSENSUS

Standardized evaluation methodology for renal cortical blood perfusion in elderly patients using contrast-enhanced ultrasound: A Chinese expert consensus (2024 edition)

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Funding information
Basic Research Project of the Central Academy of Medical Sciences of China, Grant/Award Number: 2019PT320012; Capital Clinical Diagnosis and Treatment Technology Research and Translation Application, Grant/Award Number: Z211100002921011; National High Level Hospital Clinical Research Funding, Grant/Award Number: BJ-2018-198 and BJ-2022-089; Beijing Health Science and Technology Achievements and Appropriate Technology Promotion Project, Grant/Award Number: BHTPP2022076

Abstract

As a sensitive and non-invasive method for assessing changes in renal cortical blood perfusion in the elderly, contrast-enhanced ultrasound (CEUS) can indirectly reflect changes in kidney filtration and reabsorption function, thus providing feasibility for early evaluation of renal function changes. However, significant differences exist among researchers in terms of operational methods, contrast agent selection, post-data analysis, and many other aspects, leading to substantial heterogeneity in results. This hinders horizontal comparisons and greatly limits the clinical application of contrast-enhanced ultrasound for evaluating renal cortical blood flow perfusion. Based on the latest domestic and overseas literature and discussions with clinical experts, this consensus provides recommended guidelines for the evaluation of renal cortical blood flow perfusion using contrast-enhanced ultrasound. It is hoped that this consensus will promote a better understanding of CEUS among medical practitioners at all levels and standardize the examination of renal cortical blood flow perfusion with CEUS.

KEYWORDS
CEUS, consensus, kidney perfusion

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In 2017, the global prevalence of chronic kidney disease (CKD) was estimated at 9.1% (approximately 698 million individuals), with approximately132 million cases reported in China.[1] The elderly populations are particularly susceptible to various forms of CKD, often presenting with covert symptoms, numerous complications, and unfavorable prognoses. It is therefore imperative that changes in renal function are identified at an early stage. Conventional laboratory tests, including measurements of urinary protein and serum creatinine, frequently fail to reveal significant alterations in the initial stages of disease progression and are incapable of evaluating the functionality of each kidney independently. Radionuclide renal dynamic imaging, despite its recognition as the most sensitive modality for separate renal function assessment, radionuclide renal dynamic imaging carries the drawback of radiation exposure. Renal tissue biopsy remains the gold standard for the diagnosis of renal pathologies; however, its invasive nature renders it unsuitable for the ongoing monitoring of renal functional changes.

The relationship between the onset, progression, and prognosis of various renal disease, including glomerular, interstitial, and vascular pathologies—and alterations in renal cortical blood perfusion has been well documented.[2] Recently developed, contrast-enhanced ultrasound (CEUS) represents a semi-quantitative, sensitive, and non-invasive approach for evaluating these perfusion changes. CEUS has been demonstrated to enhance the accuracy of diagnosing renal artery stenosis and facilitate a comprehensive evaluation of renal cortical blood perfusion parameters in a single session, this approach allows for the depiction of the perfusion state of the renal cortex. The analysis of dynamic CEUS images yields fitted time-intensity curves (TIC) and associated perfusion metrics such as peak intensity (PI), time to peak (TTP), mean transit time (MTT), wash-in rate (WiR), and area under the curve (AUC). It has been demonstrated that deviations in these parameters frequently precede the alterations detected through conventional biochemical markers, such as serum creatinine[3] and bear relevance to glomerular pathology.[4] Variations in renal cortical blood perfusion indirectly reflect changes in renal filtration and reabsorption capabilities,[5] which playing a critical role in the pathogenesis and evolution of diverse renal disorders. Such parameters are instrumental in the early evaluation of renal impairment,[6] underlining the potential of CEUS in both direct and indirect assessments of renal function alterations.

In 2021, after extensive discussions with domestic experts, the Ultrasound Physicians Branch of the Chinese Medical Association, following extensive discussions with domestic experts, published the "Chinese Expert Consensus on Renal Artery Contrast-Enhanced Ultrasound Examination Methods and Procedures (2021 Edition)",[7] establishing a consensus on the methodologies and protocols for renal artery contrast-enhanced ultrasound examinations. Despite this achievement, a standardized approach for the quantitative assessment of renal cortical blood perfusion using CEUS remains undeveloped, with considerable variation in operative techniques, choice of contrast agent, and data analysis strategies among researchers. This diversity leads to significant heterogeneity in results, rendering comparisons across studies challenging and limiting the clinical utility of CEUS for quantitative renal cortical perfusion assessment. Consequently, the establishment of a standardized and normalized CEUS assessment protocol for renal cortical blood perfusion is critically needed.[8] This consensus was achieved by convening experts from related fields (including ultrasound, nephrology, vascular surgery, cardiology, etc.) in China to form an expert consensus committee. The committee conducted searches in various databases, such as Medline and Wanfang Data. The English search terms used were ([renal] AND [perfusion]) AND ultrasound* and ([renal] AND [perfusion]) AND sonography, whereas the Chinese search terms were kidney and CEUS. The publication time frame was set from any time to April 2023. A draft of the consensus was written and subjected to several rounds of discussion and voting by the expert committee until consensus was reached. This consensus synthesizes recent literature and expert clinical discussions to recommend standardized CEUS assessment procedures for renal cortical blood perfusion, with the aim of increasing acceptance of the technology in medical practice, streamlining CEUS examinations of renal cortical blood perfusion, supporting the comprehensive assessment of renal cortical blood perfusion in the elderly, and promoting accurate clinical diagnosis and management.

1 | Question 1: *Which patients are candidates for renal cortical blood perfusion CEUS? What preparatory measures should patients undertake prior to the contrast-enhanced ultrasound?*

Patients with various acute and chronic renal disease,[9–11] such as diabetic nephropathy,[4,12] IgA nephropathy,[13,14] altered renal function in transplant kidneys,[15,16] and post-surgical kidneys,[17] alongside various renal vascular disease such as Takayasu arteritis,[18] atherosclerotic renal artery stenosis,[19] and post-renal artery stenting,[20,21] are suitable for the quantitative assessment of renal cortical blood perfusion using contrast-enhanced ultrasound. Patients undergoing CEUS for renal cortical blood perfusion alone do not require any special preparation. However, those requiring simultaneous assessment of renal artery status and accessory renal arteries should fast beforehand.[22] Elderly patients with experiencing constipation might benefit from a carminative the day prior to the examination to alleviate intestinal gas obstruction, if significant abdominal distension is present. It is advised that during the contrast phase, patients maintain calm breathing or hold their breath during the initial arterial phase (pre-contrast training can be provided) to limit renal movement and ensure its stable positioning within the ultrasound image, thereby improving the accuracy of quantitative CEUS analysis.[4,23] In addition, comprehensive pre-contrast communication with patients is essential to clarify the examination's purpose, methodology, estimated duration of the study, to inquire about any allergies, to discuss potential complications, and to secure patient cooperation and informed consent.

Recommendation: *Patients with clinical suspicion of renal dysfunction or renal vascular disease are suitable candidates for CEUS renal cortical blood perfusion CEUS examinations. Besides pre-procedure respiratory training, specific preparations based on the examination requirements should be undertaken, with a strong emphasis on the thorough communication and signing of informed consent.*

2 | Question 2: *Is it necessary for patients to manage their blood pressure prior to contrast? Considerations for obese patients during the examination*

The effect of blood pressure on the quantitative analysis of renal cortical blood perfusion in CEUS remains uncertain, although some studies suggest that patients' blood pressure should be regulated to less than 140/90 mmHg and greater than 100/60 mmHg before the procedure.[3,8] Research indicates that a patient's weight significantly influences the quantitative analysis of renal cortical blood perfusion CEUS, as the ultrasound probe's penetration capability of the ultrasound probe decreases with depth, adversely affecting image quality.[24]

Recommendation: *It is recommended that patients follow previous medical guidance to control their blood pressure prior to the contrast procedure. For overweight patients, adjustments to equipment parameters (such as increasing image depth, decreasing probe frequency, and modifying the focus positions) may facilitate a clear delineation of the renal outline, thereby allowing CEUS renal cortical blood perfusion studies to be performed.*

3 | Question 3: *What ultrasound contrast agents are commonly used?*

Currently, the ultrasound contrast agents approved for clinical use in China include sulfur hexafluoride microbubbles for injection (brand name: SonoVue, Bracco SpA Milan, Italy,), perflubutane microbubbles for injection (brand name: Sonazoid, USA,GE Healthcare), perfluoropropane albumin microsphere injection (brand names: Xue Ruixin, China Hunan, Runkun Pharmaceutical; Li Daxing, Lizhuo Pharmaceutical Co., Ltd., China Xiamen; Xin Su, Yangtze River Pharmaceutical Group, China Jiangsu), and perflutren lipid microspheres injection (brand name: DEFINITY, Lantheus Medical Imaging, USA).

In clinical practice, ultrasound contrast agents such as SonoVue® (Milan, Italy, Bracco SpA) and Sonazoid® (USA, GE Healthcare) are commonly used, with SonoVue being predominantly utilized for renal cortical blood perfusion imaging. SonoVue, a pure blood pool contrast agent,[25] consists of microbubbles with an average diameter of 2.5 µm, mirroring the size of red blood cells. When administered intravenously, these microbubbles disseminate throughout the organ tissues. SonoVue microbubbles are encased in a monolayer phospholipid shell with sulfur hexafluoride (SF6), an inert, non-toxic gas, encapsulated within. SF6 is rapidly eliminated via pulmonary circulation, with over 80% detectable in exhaled air within 2 min post-injection, and nearly all detectable after 15 min.[26] Because of its pulmonary metabolism and lack of hepatorenal toxicity, SonoVue is particularly suitable for patients with hepatic or renal impairment.[27] Sonazoid differs from pure blood pool contrast agents in that, in addition to the arterial and portal phases,[28] it exhibits a delayed phase starting 5–10 min following injection. The mechanism involves Sonazoid microbubbles being phagocytosed by the reticuloendothelial system, specifically by Kupffer cells in the liver.[29,30] The outer shell of Sonazoid consists of Sodium hydrolyzed phosphatidylserine, whereas the interior contains the inert and non-toxic gas perfluorobutane. Approximately 50% of the perfluorobutane is exhaled within half an hour following injection, and 96% is exhaled within 24 h.[31,32] The phospholipid shell is metabolized by the liver and eliminated by the liver (biliary excretion) and/or the kidneys (urinary excretion).[33]

Common side effects, such as headaches, nausea, and reactions at the injection site, have a comparable or lower incidence rate than those associated with other contrast-enhanced imaging procedures.[34] Before using ultrasound contrast agent, inquire about the patient's allergies and past history, and establish an emergency plan for managing adverse reactions. In the event of an adverse reaction, promptly follow the established treatment plan.[35–37]

Recommendation: *SonoVue is recommended as the preferred ultrasound contrast agent for renal cortical blood perfusion, with strict adherence to the recommended indications and contraindications to avoid adverse reactions.*

4 | Question 4: *How should ultrasound contrast agents be administered?*

SonoVue is frequently used for renal cortical blood perfusion imaging in clinical settings.[4,38] Following strict guidelines, 5 mL of 0.9% sterile sodium chloride solution is introduced into the vial prior to use, followed by vigorous shaking for 20 s to ensure that the lyophilized powder is fully dispersed, creating a homogenous white emulsion for microbubble suspension. The vial must be vortexed prior to aspiration to evenly redistribute the microbubbles, which should then be promptly administered immediately after aspiration. SonoVue is typically administered via peripheral venous access, often via the elbow vein,[24,39] though central venous routes have also been uesd.[40] It is commonly administered as a bolus injection.[12,39,41] The dosage of SonoVue for renal cortical blood perfusion varies across studies, with a majority opting for a fixed dose[4,24,42] and others adjusting based on patient weight.[10,43] Fixed dosages range from 0.5 mL[8,41] to 2.0 mL,[40,44,45] with 1.2 mL as a frequently chosen dose.[46–48] When dosing is adjusted for patient weight, a common standard is 0.02–0.03 mL/kg.[49,50] For an adult weighing 60 kg, this calculation approximates a dosage of 1.2–1.8 mL, aligning closely with the fixed dosage.

Recommendation: *Ultrasound contrast agents must be prepared and utilized in strict accordance with to the guidelines provided. It is recommended that the agent be administered as a bolus injection through the elbow vein, at a dosage of 1.2 mL per kidney, followed by a 5 mL saline flush. Following administration, patients should be kept under close medical observation for at least 30 minutes to ensure safety and to monitor for any adverse reactions.*

5 | Question 5: *How should ultrasound equipment parameters be adjusted for renal cortical blood perfusion CEUS?*

Ultrasound systems equipped with an abdominal sector probe and CEUS functionality are generally suitable for conducting renal cortical blood perfusion CEUS examinations. The frequency range for abdominal convex probes typically spans 1–7 MHz. As ultrasound devices vary across manufacturers, so do the parameters, which can be optimized by technologists to meet clinical needs and improve CEUS results. To minimize the loss of contrast agent microbubbles, the mechanical index (MI) is set lower, typically around 0.06–0.08 in most studies.[10,13,45,51] Although there are no universally prescribed settings for other ultrasound parameters, adjustments should be made by technicians based on the device's capabilities of the device to ensure optimal visualization of the kidney, including adjustments to depth and focus, with some settings extending the depth to 14–16 cm.[23]

Recommendation: *The necessity for dedicated ultrasound equipment for renal cortical blood perfusion CEUS is minimal, provided the device is equipped with an abdominal sector probe and CEUS capability. An MI setting in the range of 0.06–0.08 is recommended, with flexibility to adjust other parameters according to clinical needs. For consistency in comparative studies, it is advisable to maintain consistent equipment settings throughout the research period.*[52]

6 | Question 6: *What is the optimal duration for dynamic image capture in renal cortical blood perfusion CEUS, and what should be the interval between imaging both kidneys?*

Clinical experience indicates that the contrast agent (SonoVue) is predominantly cleared from the kidneys within 2–3 min, aligning with the majority of studies that set the image capture duration at 3 min.[38,46,52,53] A minority of studies report shorter[24,39] or longer[11] durations. The interval for conducting CEUS on both kidneys primarily depends on the contrast agent's metabolic rate. To minimize the impact of residual contrast from prior administrations, subsequent imaging should only proceed once the agent has undergone substantial metabolism. In was demonstrated that SonoVue typically undergoes complete metabolism within approximately 15 min, corroborated by several studies,[11,49,52] with a few exceptions where intervals were less than 15 min.[24]

Recommendation: *The collection period for dynamic images should encompass the full course of renal cortical blood perfusion imaging, with a recommended duration of 3 minutes per kidney, timed from the moment of contrast agent bolus injection. At least a 15-min interval is advised between imaging sessions for each kidney in order to ensure accurate assessments.*

7 | Question 7: *What positions should patients assume during renal cortical blood perfusion CEUS?*

Typical positions for kidney examinations include supine, lateral, and prone. During renal cortical blood perfusion CEUS, the choice of position largely mirrors standard practices to ensure comprehensive and clear visualization of the kidney's largest coronal section. The majority of research uses lateral positioning,[20,23,38] with fewer instances of supine[45] and prone positions.[13] It's crucial during dynamic image collection to maintain the kidney's longitudinal axis perpendicular to the ultrasound beam, thus ensuring image stability and minimal displacement due to breathing.

Recommendation: *For right renal cortical blood perfusion CEUS, the left lateral position is recommended, and vice versa for the left kidney. In cases where the examinee is unable to maintain a lateral position, the use of lumbar and back support cushions is suggested to optimize both operator ease and patient comfort, thereby enhancing image quality.*

8 | Question 8: *What considerations are essential during dynamic image collection for renal cortical blood perfusion CEUS?*

The primary objective of dynamic image collection for renal cortical blood perfusion CEUS is to facilitate subsequent quantitative analysis, either on the machine or using offline software. It is of the utmost importance to ensure stable imaging and to maintain the region of interest (ROI) within the renal cortex throughout respiratory movements are critical for accurate analysis. Some offline software may necessitate marking a reference area at the same depth and size as the ROI but outside the renal cortex; thus, it's important to choose a section that allows sufficient space around the kidney for this purpose.

Recommendation: *The examiner should secure the probe, while the examinee should maintain a stable position and breathe evenly, aligning the kidney's long axis parallel to the probe as much as possible. The chosen imaging section should present the kidney in a horizontal orientation, allowing for the comprehensive visualization of the renal parenchyma. When using software that necessitates the selection of a reference area, it is imperative to ensure that a section is selected that accommodates suitable soft tissue at either the kidney's upper or lower pole at the same level as the reference area.*

9 | Question 9: *How is the analysis conducted post-collection of dynamic images for renal cortical blood perfusion CEUS?*

Analysis software utilized in both domestic and international studies can be divided into two categories: on-machine analysis software integrated within ultrasound systems provided by manufacturers[8,11,13,47] such as GE, Samsung, Canon, etc., and independent offline analysis software[12,24] such as Sonoliver, Vuebox, etc., which operates irrespective of the ultrasound machine model. Both software types are capable of analyzing dynamic renal cortical blood perfusion images to derive the time-intensity curve (TIC) and associated parameters. For instance, software integrated within ultrasound systems, such as that provided by Samsung, enables users to directly access the TIC interface to delineate the ROI, select a fitting model, and proceed with quantitative analysis upon completion of dynamic image storage. In the case of offline software such as Vuebox, DICOM format images are imported, allowing users to specify the workspace, outline the ROI, and choose the frame rate and fitting model for subsequent analysis.

Recommendation: *Selection of the appropriate analysis software should be aligned with the available equipment, clinical requisites, and research objectives. Given the variability in analysis parameters and modalities across different software, it is advised that single-center studies consistently utilize one type of analysis software. Conversely, multicenter studies should strive for uniform imaging condition settings, standardized image collection techniques, and a singular offline software platform for analysis to ensure comparability.*

10 | Question 10: *Are there any considerations to be made regarding the delineation of the Return on Investment (ROI) in image analysis?*

During dynamic image collection for renal cortical blood perfusion CEUS, it is inevitable that kidney movement due to respiration is inevitable, rendering the selected ROI static within the moving image. Consequently, there's relative displacement between the ROI and the renal cortex. The ROI should be positioned in a segment consistently within the renal cortex throughout respiratory cycles, often in the central cortical area as documented by numerous studies.[14,54] With regard to the size of the ROI size, analysis software offers options for shape selection and displays the area, with some studies[39] opting for an ROI size of approximately 5–10 mm^2, others[55] choosing sizes around 60–100 mm^2, and some encompassing the entire renal cortex.[7] Typically, studies select an ROI area of about 20–30 mm^2, equivalent to a 5 mm × 5 mm rectangle or a circle with a 5 mm diameter.[13,20,47,49]

Recommendation: *The ROI should be strategically placed in the central, straight portion of the renal cortex to ensure its constant presence within the cortical region during respiratory movements. An ROI size of approximately 20–30 mm^2 is recommended; however, adjustments should be made for atrophic kidneys or thinning cortex. To enhance consistency, it is advisable to maintain uniformity in ROI positioning and sizing throughout the study is advisable.*

11 | Question 11: *Understanding the Quality of Fit (QOF) in Time-Intensity Curve (TIC) Analysis?*

The original TIC is typically presented in a jagged form, plotted with time as the horizontal axis and the ultrasound contrast agent's intensity within the ROI at various timestamps as the vertical axis. Mathematical modeling and analysis software can be used to smoothen the curve, with a higher QOF suggesting a closer match between the fitted and original curves, implying more accurate outcomes. Factors influencing QOF include contrast condition adjustments, contrast agent dosage, respiratory motion extent, circulatory status, and selections of ROI positioning and size, as well as the quantitative analysis model. Studies predominantly set QOF criteria above 75%,[51] with a few exceeding 85%,[53] and a small number aiming for above 90%.[24]

Recommendation: *For enhanced result accuracy, QOF should ideally exceed 75%. The utilization of software for renal cortical blood perfusion analysis necessitates the maintenance of consistent contrast preset conditions, the selection of an appropriate workspace, the choice of an optimal fitting model, and the adjustment of the frame rate. Minor adjustments to the ROI's position within the renal cortex's middle section and slight modifications to its size within predetermined limits for multiple fittings are recommended, followed by selecting the curve with superior fit. Segmental image instabilities caused by uncontrollable factors such as patient coughing or probe slippage should be excised to avoid significant deviations impacting the QOF.*

12 | Question 12: *What parameters are derived from analysis software?*

Diverse on-machine and offline analysis software, each using unique algorithms and mathematical models, produce various renal cortical blood perfusion parameters. Consequently, identical parameters may be interpreted in different interpretations across software platforms. The parameters that can be obtained from analysis software typically include: (1) Peak Intensity (PI), reflecting the highest signal strength of the contrast agent within the ROI, indicative of the maximum contrast agent dosage attained in that area. (2) Time to Peak (TTP), defined as the duration from when the contrast agent enters the ROI to when its intensity maximizes. (3) Mean Transit Time (MTT), defined as the interval from the contrast agent's appearance in the ROI to a 50% reduction in its peak intensity. (4) Rise Time (RT), defined as the period during which the contrast agent's intensity to escalate from 10% to 90% of its peak value. (5) Wash-in Area Under the Curve (WiAUC), representing the area under the TIC curve from the contrast agent's entry into the ROI to its peak intensity. (6) Wash-out Area Under the Curve (WoAUC), denoting the area under the TIC curve from peak intensity to the contrast agent's clearance. (7) Area Under the Curve (AUC), which represents the total area under the TIC curve from the contrast agent's entry into the ROI to its clearance, combining WiAUC and WoAUC. (8) Wash-in Rate (WiR), the steepest slope of the TIC curve during the wash-in phase. (9) Wash-out Rate (WoR), the steepest slope of the TIC curve during the wash-out phase.

Recommendation: *Parameters such as PI, TTP, MTT, RT, and AUC are extensively utilized in contemporary clinical research. PI typically correlates with the volume of blood flow in the renal cortex, while AUC relates to the contrast agent's distribution volume of the contrast agent, the velocity of blood flow, and the duration of perfusion. The selection of parameters should be tailored to the specific objectives of the study.*

13 | Question 13: *What are the limitations of quantitative analysis in renal cortical blood perfusion CEUS?*

First, as a subset of ultrasound examinations, renal cortical perfusion CEUS is subject to inherent limitations of the modality, including patient-specific abdominal imaging conditions (e.g., obstruction by intestinal gas or ribs), operator bias, and variances in ultrasound equipment and settings. Furthermore, individuals with severe cardiac or pulmonary conditions may find this examination to be intolerable. Second, the technique provides a sectional view and thus cannot encapsulate the complete blood flow dynamics of the entire renal cortex. Additionally, respiratory movements lead to shifts between the ROI and the renal cortex. Despite the availability of analysis software offering respiratory motion compensation, maintaining a constant representation of renal cortical blood perfusion in the ROI remains challenging. Presently, there is a paucity of large-scale studies examining renal blood perfusion in patients with chronic kidney disease patients using CEUS are scarce on a global scale, and research into the correlation between renal blood perfusion and renal pathological changes in such disease requires further investigation. A comprehensive comparison with pathological findings and an in-depth understanding of the imaging characteristics of patients with chronic kidney disease patients are essential for optimizing CEUS's clinical utility in diagnosing and treating chronic kidney disease.

14 | CONCLUSION

The consensus recommendations collectively emphasize the importance of a standardized approach to renal cortical blood perfusion CEUS, from patient selection and preparation through to post-imaging analysis. Ensuring patient safety, optimizing imaging parameters, and utilizing consistent analysis methodologies are pivotal for achieving reliable and accurate renal function assessments (Figure 1). This streamlined approach to CEUS aims to enhance diagnostic precision, facilitate

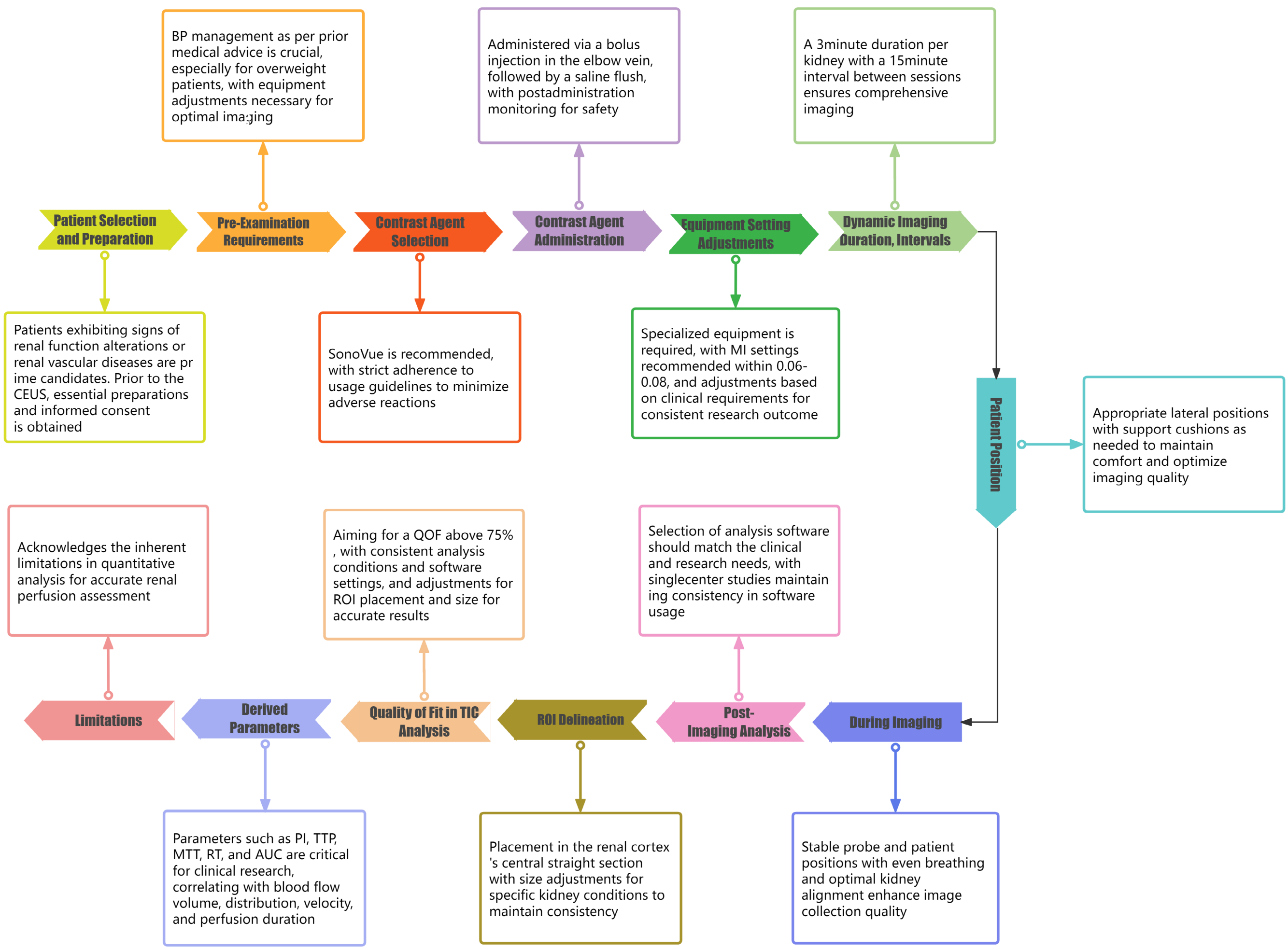

FIGURE 1 Streamline of CEUS examination for renal cortical blood perfusion.

early detection and management of renal disease, and ultimately contribute to the advancement of nephrology research and patient care. Significantly, the application of CEUS in quantitative analyses offers a substantial contribution towards the objective appraisal of renal microvascular perfusion. This facilitates the early identification of renal function deterioration, continuous monitoring, and the dynamic assessment of therapeutic outcomes, thereby standardizing the utilization of CEUS can be standardized to augment both the precision and the dependability of renal evaluations—factors that are paramount for the enhancement of patient care and disease management strategies.

This consensus anticipates the future, highlighting the contemporary importance of CEUS and laying a solid groundwork for its subsequent evolution and wider application within the field of nephrology and related disciplines. With the advent of technological progress and more profound understanding of renal pathophysiology, CEUS is expected to become increasingly essential in the diagnosis and management of renal conditions. This advancement holds the potential for significantly enhanced health care outcomes, particularly for the geriatric population. Therefore, the consensus serves as a foundational pillar for the future trajectory of CEUS, poised to propel forward the domain of patient care and inaugurate new prospects for its utilization across varied patient groups, securing its role as a pivotal cornerstone in the evolving landscape of renal function management among the elderly.

ACKNOWLEDGMENTS

There was no acknowledgement.

FUNDING INFORMATION

The National High level Hospital Clinical Research Business Special Guideline Project (BJ-2022-089), Beijing Health Science and Technology Achievements and Appropriate Technology Promotion Project (No. BHTPP2022076), Capital Clinical Diagnosis and Treatment Technology Research and Translation Application (No. Z211100002921011), The National High level Hospital Clinical Research Funding (No. BJ-2018-198), and Basic Research Project of the Central Academy of Medical Sciences of China (2019PT320012).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

ETHICS STATEMENT

This study did not involve human subjects and obtained an ethical exemption from Beijing Hospital.

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How to cite this article: Junhong R, Wen H. Standardized evaluation methodology for renal cortical blood perfusion in elderly patients using contrast-enhanced ultrasound: A Chinese expert consensus (2024 edition). *Aging Med*. 2024;7:429-437. doi:10.1002/agm2.12345

APPENDIX A

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