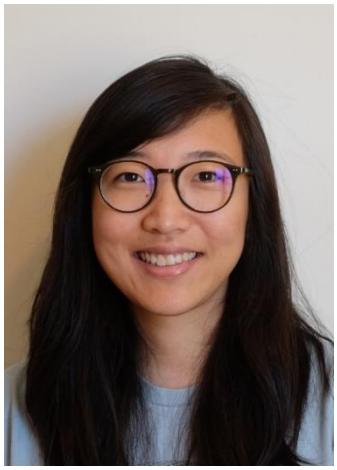
Submission to The Tantalum-Niobium International Study Center for *The 2024 Anders Gustav Ekeberg Prize for Innovation in Tantalum*

Benjamin M. Yeh, MD is a Professor in the Abdominal Imaging Section in the Department of Radiology at the University of California, San Francisco and an internationally recognized expert in novel computed tomography (CT) contrast agents and multi-energy CT imaging. Dr. Yeh's research focuses on abdominopelvic CT imaging, including the development of image post-processing algorithms, novel CT imaging techniques, oncologic imaging, bowel imaging, and novel CT contrast materials such as **orally administered and intravenously injected tantalum oxide nanoparticles**. Dr. Yeh is interested in transforming the diagnostic capabilities of CT with over 220 peer-reviewed manuscripts, most on contrast enhanced abdominopelvic CT, and served as PI on five NIH grants (>$12M) to study CT contrast agents. Ongoing projects include the development and testing of novel contrast-enhanced imaging techniques for CT, including dual energy CT, and novel contrast materials for oncologic imaging using both silica microparticles and **tantalum oxide nanoparticles**.

Peter J. Bonitatibus Jr., PhD is an Associate Professor of Chemistry in the Department of Chemistry and Chemical Biology at Rensselaer Polytechnic Institute. As a synthetic inorganic chemist with 30 years of experience in the synthesis and characterization of inorganic coordination complexes, homogeneous catalysts, and nanoparticles, Prof. Bonitatibus is credited with conceiving a CT contrast agent platform technology that uses **tantalum oxide core-shell nanoparticles**. Prof. Bonitatibus was the lead author on the first scientific paper that described a zwitterionic injectable **tantalum oxide nanoparticle-based CT imaging agent**, that has since been developed through chemical process optimization (kilogram scale synthesis and purification) and GLP animal studies with NIH support from multiple grants with Dr. Yeh (2013 to present day). Prof. Bonitatibus, Dr. Yeh, and Yuxin Sun have been collaborating since 2013 to advance the clinical translation of a **tantalum oxide-based contrast agent** for improved diagnostic CT imaging and patient safety.



Yuxin Sun, MS is a Research Associate in the Department of Radiology at the University of California, San Francisco (UCSF) and Lab Manager at the Contrast Material and CT Translational Research Laboratory at UCSF. Yuxin explores novel contrast-enhanced imaging techniques for CT, including dual energy CT, using **tantalum oxide-based CT contrast agents** provided by Prof. Bonitatibus. Ongoing phantom imaging and preclinical projects develop and validate new CT techniques and develop novel contrast agents to dramatically improve patient diagnoses, presurgical planning, and treatment monitoring.

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We are delighted to submit this application to The Tantalum-Niobium International Study Center for *The 2024 Anders Gustav Ekeberg Prize for Innovation in Tantalum* and nominate this team that has been collaborating for more than ten years to advance the clinical translation of a **tantalum** oxide nanoparticle-based contrast agent for improved diagnostic CT imaging capabilities and patient safety through extensive non-GLP and GLP preclinical development, safety tests, and efficacy tests.[1-15]

Despite the need for ionizing radiation exposure, the clinical value of CT is such that over 40 million contrast-enhanced scans are performed annually in the United States and it is the imaging modality of choice for numerous disease diagnosis. Unfortunately, only one class of clinical CT contrast agent is available, namely small-molecule tri-iodinated derivatized benzene-ring agents (**Figure 1**). These agents all show, (1) reduced CT signal when imaged in thicker anatomy such as the torso, particularly in the obese patient population; (2) poor evaluation of vasculature due to short intravascular half-life from so-called 'washout' or the rapid nonspecific redistribution from blood plasma to interstitial fluid; (3) similar appearance to vascular calcifications or metal implants such as stents; and (4) cross reactivity, such that patients intolerant to one iodine agent are intolerant to the entire class. No substantively new intravenous CT contrast agent has been introduced in over 40 years.

Elemental **tantalum** and its oxide are biologically safe and have long been used in medical implants. From an X-ray physics standpoint, **tantalum** gives substantially higher attenuation than iodine at the X-ray tube voltages (kVp) of 100 kVp and higher typically used to scan most patients, particularly the obese patient population. Contrast-enhanced CT stands to be revolutionized through further development (clinical trials) of this team's **tantalum** nanoparticle-based intravascular contrast agent (**Figure 1**) that provides unprecedented vascular delineation in comparison to clinical iodine-based agents regardless of patient body habitus, e.g, mouse, rat, rabbit, or swine.[1,3,7] This is due, in part, to **innovative structural engineering and chemical manipulation and of tantalum nanoparticle core-size and coating** that has been demonstrated to control the agent's biological retention, blood pool distribution, and pharmacokinetics.[7,8] The team's tantalum oxide nanoparticle so-called '**TaCZ**' is coated with a carboxybetaine zwitterionic (CZ) shell that is stable to an exceptionally wide range of pH and autoclave conditions.[7] The innovative CZ shell imparts water solubility and features distributed charges but is overall charge neutral, thereby avoiding potential cytotoxicity concerns associated with cationic coatings. This zwitterionic character gives low viscosity and osmolality, promotes rapid renal clearance, and negligible organ retention.

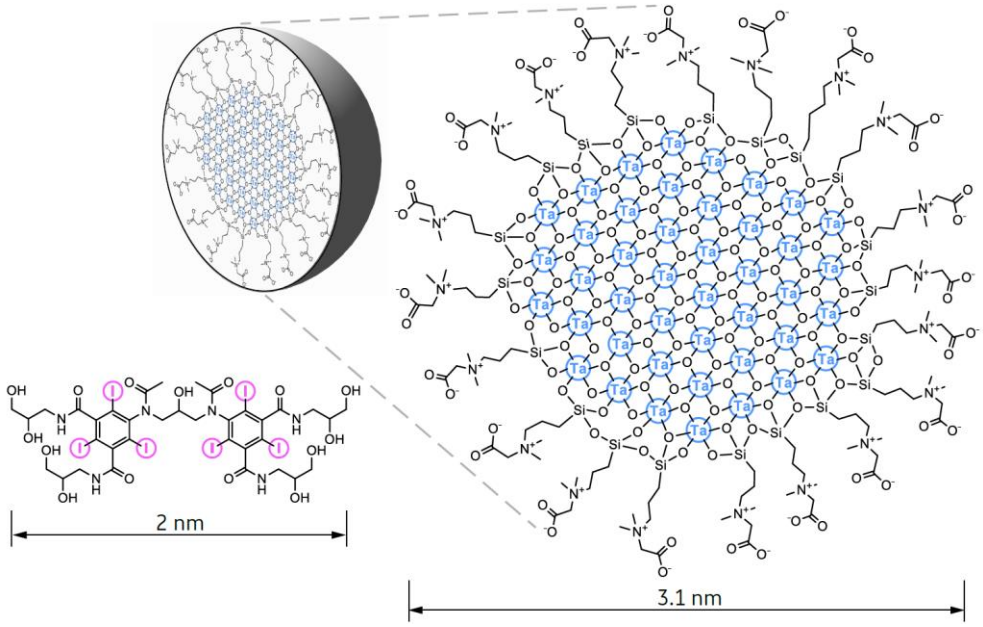


Figure 1. Relative sizes of iodixanol and tantalum agent (TaCZ). Iodine atoms are in magenta; tantalum atoms are in blue. Note that iodixanol is roughly planar, whereas TaCZ is approximately spherical as a nanoparticle.[7-8,10-12]

Intravenous dose injection of **TaCZ** in swine, rats, and rabbits showed no obvious toxicity. High dose rat intravenous injection of 5000 mg Ta/kg showed no obvious toxicity (10X intended human intravenous dose). Oral dosing of 500 mg Ta/kg (3X intended human oral dose) shows minimal blood uptake, with no **tantalum** detected after 24 hours in rats. Intraperitoneal dosing of **TaCZ**, simulating leakage from bowel, showed rapid bodily resorption without obvious toxicity. Profoundly, the biological half-life of **TaCZ** agent is on par with that of small molecule iodinated agents. This discovery is extraordinary since blood pool agents generally have a very long half-life, on the order of days. Unlike prior contrast agents that show blood pool distribution, the **TaCZ** agent this team designed, developed, and tested appears to be "just right" in terms of size at ~3 nm and zwitterionic surface coating, i.e., small enough to be filtered rapidly through the renal collecting system, yet large enough to remain in the blood pool without crossing normal vascular endothelial junctions or showing retention in reticuloendothelial tissues. Indeed, ~99% of injected **tantalum** as **TaCZ** was shown to be eliminated after 48 hours of a bolus-injected dose of 500 mgTa/kg in rat, which is equivalent to clinical iodine agent elimination. *No other injectable nanoparticle formulation for CT (from academia or industry) is known to match this* ***team's innovation*** *in terms of* ***TaCZ*** *agent biological safety (clearance) coupled with clinically relevant physicochemical properties of concentrated agent solutions, e.g., viscosity and osmolality.*

Imaging studies with **TaCZ** showed superior opacification than iodine particularly above 100 kVp in phantoms and swine (**Figure 2**).[1,3,7,9] More profoundly, this team's **tantalum agent** features a CT attenuation profile that is visibly different from vascular calcifications unlike today's commercial iodine-based agents. The novel **tantalum** agent is designed to appear as a different "color" than iodine (or barium or gadolinium) agents at dual energy CT (DECT).[15] When given simultaneously with iodine at DECT, the **tantalum** agent gives high-resolution perfectly co-registered CT delineation of intertwined anatomy in a single 5-second information-rich CT scan without added radiation dose (**Figure 3**).[2] Since approximately 10-20% of current clinical CT scanners in America are DECT capable and approximately 40% of scanners

are expected to have DECT capability by 2026, introduction of the team's **tantalum** agent will catalyze a "color" revolution for multi-contrast multi-energy CT imaging, analogous to the introduction of color television to the grayscale world.[5]

We envision vivid clinical CT contrast agents that are different "colors" from each other to give unprecedented detailed multi-color-contrast CT images for greater accuracy and speed of anatomic diagnosis in a general utility setting and for delineation of a broad range of disease. We feel our work with tantalum as a CT imaging agent, particularly in 2023, is progress to unlock powerful diagnostic abilities of multi-energy CT and transform the capability of CT for oncologic imaging.

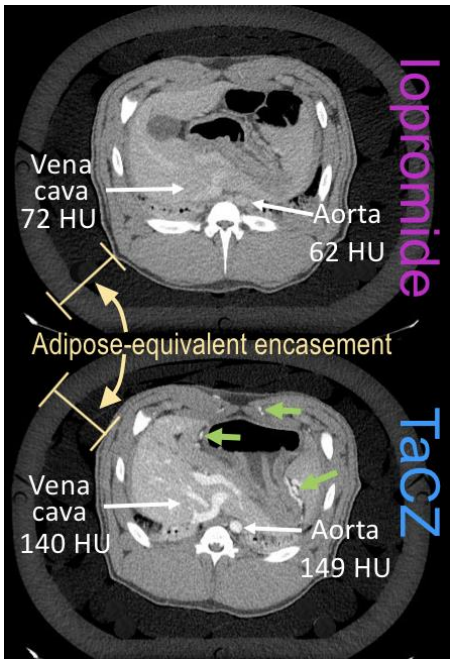


Figure 2. Vascular delineation at CT in swine encased within adipose-equivalent rings to simulate obese patient size, imaged 80 sec after intravenous **500 mg iodine/kg** versus **500 mg Ta/kg** bodyweight. Intravascular iodine signal (iopromide) is faint; tantalum vascular signal (TaCZ) is vivid. Small vessels (green arrows) are revealed only on the TaCZ image.[3]

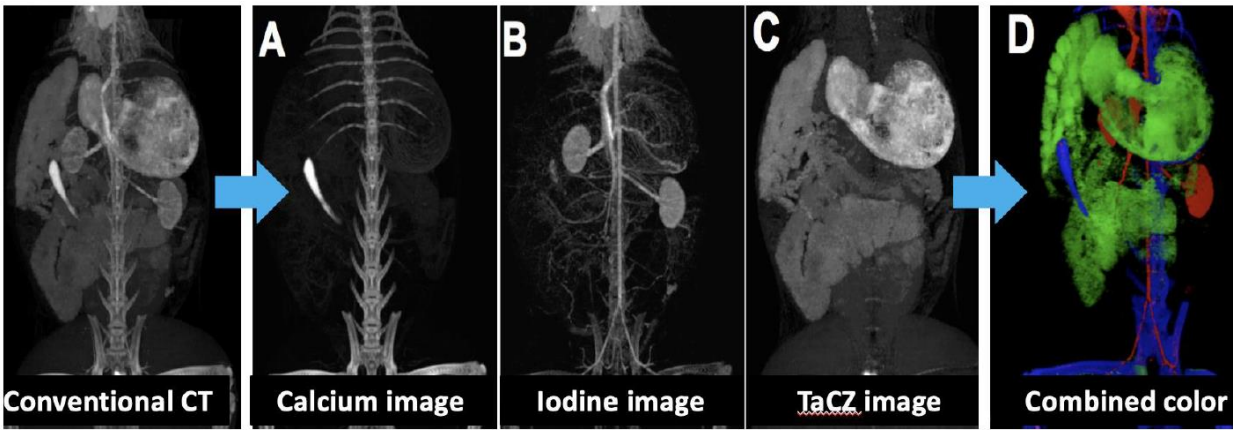


Figure 3. Oral TaCZ with intravenous iodine contrast enhanced DECT of rabbit. (Left) is readily decomposed into individual high resolution (A) calcium bone; (B) iodine vascular; (C) TaCZ bowel images and recombined in (D) color to intuitively clarify anatomic relationships. With TaCZ, any clinical MECT scanner can give similar image reconstructions without need to upgrade either the scanner hardware or software. Based on material X-ray attenuation at low versus high X-ray spectra, dual-energy data can be reconstructed to better evaluate bony, vascular, and bowel anatomy. These individual high-resolution images can then be recombined into 3D composite color image (D), set to show fine inter-relationships of anatomy depicted by each map.[2]

References and Nominee's Key Publications:

1. Heimer MM, **Sun Y**, Grosu SR, Cyran CC, **Bonitatibus PJ**, Okwelogu N, Bales B, Meyer DE, **Yeh BM** "Novel Intravascular Tantalum Oxide-based CT Contrast Agent Achieves Improved Vascular Contrast Enhancement and Conspicuity Compared to Iopromide in an Animal Multiphase CT Protocol" Investigative Radiology 2023, Under Review.

2. **Yeh BM**, Heimer MM, **Sun Y**, **Bonitatibus PJ** "Oral CT Contrast Agents: What's New and Why?" American Journal of Roentgenology 2023, Oct 25 [published online]. DOI:10.2214/AJR.23.29970.

3. **Yeh BM**, FitzGerald PF, Colborn RE, Edic PM, Lambert, **Sun Y**, Stillson C, Marino ME, **Bonitatibus PJ** "An Intravascular Tantalum Oxide-based CT Contrast Agent: Preclinical Evaluation Emulating Overweight and Obese Patient Size" Radiology 2018, 289, 103-110.

4. FitzGerald PF, Colborn RE, Edic PM, Lambert, **Bonitatibus PJ**, **Yeh BM** "Liquid Tissue Surrogates for X-ray and CT Phantom Studies" Medical Physics 2017, 44, 6251-6260.

5. **Yeh BM**, FitzGerald PF, Edic PM, Lambert JW, Colborn RE, Marino ME, Evans PM, Roberts JC, Wang ZJ, Wong MJ, **Bonitatibus PJ** "Opportunities for New CT Contrast Agents to Maximize The Diagnostic Potential of Emerging Spectral CT Technologies" Advanced Drug Delivery Reviews 2017, 113, 201-222.

6. Lambert JW, **Yeh BM**, **Sun Y**, FitzGerald PF, Edic PM, Colborn RE, **Bonitatibus PJ** "The Effect of Patient Diameter on the Dual-Energy Ratio of Selected Contrast-Producing Elements" Journal of Computed Assisted Tomography 2017, 41, 505-510.

7. FitzGerald PF, Butts MD, Roberts JC, Colborn RE, Torres AS, Lee BD, **Yeh BM**, **Bonitatibus PJ** "A Proposed Computed Tomography Contrast Agent Using Carboxybetaine Zwitterionic Tantalum Oxide Nanoparticles: Imaging, Biological, and Physicochemical Performance" Investigative Radiology 2016, 51, 786-796.

8. Crowder JM, Bates N, Roberts JC, Torres AS, **Bonitatibus PJ** "Determination of Tantalum from Tantalum Oxide Nanoparticle X-ray/CT Contrast Agents in Rat Tissues and Bodily Fluids by ICP-OES" Journal of Analytical Atomic Spectrometry 2016, 31, 1311-1317.

9. FitzGerald PF, Colborn RE, Edic PM, Lambert JW, Torres AS, **Bonitatibus PJ**, **Yeh BM** "CT Image Contrast of High-Z Elements: Phantom Imaging Studies and Clinical Implications" Radiology 2016, 278, 723-733.

10. **Bonitatibus PJ**, Torres AS, Kandapallil B, Lee BD, Goddard GD, Colborn RE, Marino ME "Preclinical Assessment of a Zwitterionic Tantalum Oxide Nanoparticle X-ray Contrast Agent" ACS Nano 2012, 6, 6650-6658.

11. Torres AS, **Bonitatibus PJ**, Colborn RE, Goddard GD, FitzGerald PF, Lee BD, Marino ME "Biological Performance of a Size-Fractionated Core-Shell Tantalum Oxide Nanoparticle X-Ray Contrast Agent" Investigative Radiology 2012, 47, 578-587.

12. **Bonitatibus PJ**, Torres AS, Goddard GD, FitzGerald PF, Kulkarni AM "Synthesis, Characterization, and Computed Tomography Imaging of a Tantalum Oxide Nanoparticle Imaging Agent" Chemical Communications 2010, 46, 8956-8958.

13. Heimer MM, **Sun Y**, Okwelogu N, **Bonitatibus PJ**, Meyer DE, Bales B, Houshmand S, **Yeh BM** ”Benchmarking a Novel Intravascular Tantalum Oxide-based CT Contrast Agent in a Multiphase Protocol: Preliminary Results of a Preclinical Study” RöFo 2023, 195(S01), S43. DOI:10.1055/s-0043-1763058. Also presented at the German X-ray Congress; Wiesbaden, Germany; May 2023.

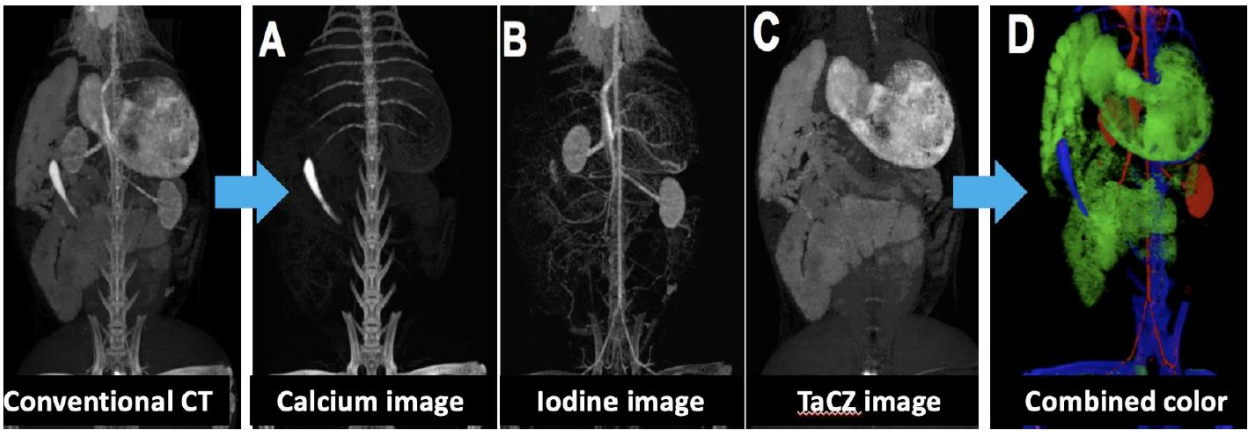
14. Heimer MM, **Sun Y**, Meyer D, Bales B, Okwelogu N, Houshmand S, **Bonitatibus PJ**, **Yeh BM** “Performance of a Novel Intravascular Tantalum Oxide-based CT Contrast for Enhancement and Conspicuity of Thoracic Vasculature in an Animal Model: Total and Relative Contrast Material Advantage” Radiological Society of North America (RSNA); Chicago, IL; November 2023.

15. **Sun Y**, Heimer MM, Yin Z, Bales B, **Bonitatibus PJ**, **Yeh BM** “Evaluation of an Experimental Tantalum Oxide Contrast Material for Material Separation from Iodine and Gadolinium using DECT and PCCT” Radiological Society of North America (RSNA); Chicago, IL; November 2023.

Nominee’s List of 2023 Abstracts - Five (5) abstracts are shown below:

Yeh BM, Heimer MM, **Sun Y**, **Bonitatibus PJ** ”Oral CT Contrast Agents: What’s New and Why?” American Journal of Roentgenology 2023, Oct 25 [published online]. DOI:10.2214/AJR.23.29970.

Current CT oral contrast agents improve the conspicuity and confidence for bowel and peritoneal findings in many clinical scenarios, particularly for outpatient and oncologic abdominopelvic imaging. Yet, existing positive and neutral oral contrast agents may diminish the detectability of certain radiologic findings, frequently in the same scans in which the oral contrast agent improves the detectability of other findings. With ongoing improvements in CT technology, particularly multi-energy CT, opportunities are opening for new types of oral contrast agents to further improve anatomic delineation and disease detection using CT. The CT signal of new dark oral contrast agents and of new high-Z oral [**tantalum**] contrast agents promise to combine the strengths of both positive and neutral oral CT contrast agents by providing distinct CT appearances in comparison with bodily tissues, iodinated intravenous contrast agents, and other classes of new CT contrast agents. High-Z [**Tantalum**] oral contrast agents will unlock previously inaccessible capabilities of multi-energy CT, particularly photon-counting detector CT, for differentiating simultaneously administered intravenous and oral contrast agents; this technique will allow generation of rich 3D, intuitive, perfectly co-registered, high-resolution image sets with individual contrast-agent "colors" that provide compelling clarity for intertwined intra-abdominal anatomy and disease processes.



Heimer MM, **Sun Y**, Meyer D, Bales B, Okwelogu N, Houshmand S, **Bonitatibus PJ**, **Yeh BM** "Performance of a Novel Intravascular Tantalum Oxide-based CT Contrast for Enhancement and Conspicuity of Thoracic Vasculature in an Animal Model: Total and Relative Contrast Material Advantage" Radiological Society of North America (RSNA); Chicago, IL; November 2023.

Purpose: To compare a novel intravenous **tantalum** oxide (TaCZ) nanoparticle CT contrast agent to conventional iodinated (iopromide) CT contrast agent for thoracic artery and vein visualization in a rabbit model.

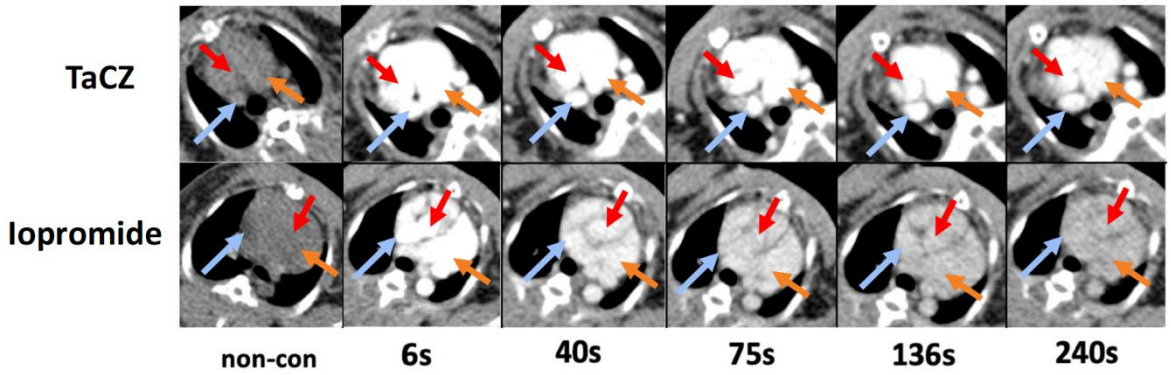
Methods and Materials: Five New Zealand White rabbits were serially placed in a human-torso-sized adipose-equivalent encasement and scanned on a clinical CT system (Philips IQon, Best, Netherlands) before and 6, 40, 75, 136, and 240 sec after intravenous injection of 540 mg element (Ta or I) per kilogram of body weight of TaCZ or iopromide. Animals were scanned twice, once with each contrast agent. Absolute contrast enhancement of the aortic arch, pulmonary trunk, superior vena cava, and subclavian vein was measured in Hounsfield Units (HU) by averaging three regions of interest drawn in the center of the lumen minus corresponding non-contrast measurements. Randomized imaging series were viewed on a clinical PACS system to rate vascular conspicuity on a 5-point Likert scale (0 = no vascular enhancement; 1 = faintly seen or visible but discontinuous; 2 = adequate contrast of main vessel, not all branches seen; 3 = good contrast of main vessel and depiction of branches; 4 = excellent contrast of main vessel and deep branches).

Results: Mean vascular enhancement was significantly higher for **TaCZ** in all examined blood vessels at all time points compared to iopromide; aortic arch at 6s (263 vs. 217; $p < 0.01$), at 40s (265 vs. 145; $p < 0.01$), at 75s (240 vs. 119; $p < 0,01$), at 136s (217 vs. 93; $p < 0,01$) and at 240s (183 vs. 73; $p < 0.01$), pulmonary artery at 6s (296 vs. 266; $p < 0.01$), at 40s (263 vs. 138; $p < 0.01$), at 75s (246 vs. 102; $p < 0.01$), at 136s (213 vs. 83; $p < 0.01$) and at 240s (174 vs. 64; $p < 0.01$)), superior vena cava at 6s (307 vs. 211; $p < 0.01$), at 40s (255 vs. 127; $p < 0.01$), at 75s (239 vs. 96; $p < 0.01$), at 136s (196 vs. 79; $p < 0.01$) and at 240s (169 vs. 49; $p < 0.01$) and the subclavian vein at 6s (280 vs. 225; $p < 0.01$), at 40s (254 vs. 111; $p < 0.01$), at 75s (236 vs. 86; $p < 0.01$), at 136s (205 vs. 67; $p < 0.01$), and at 240s (170 vs. 54; $p < 0.01$). The mean vascular enhancement of TaCZ at a 136s delay provided comparable results to the 6s arterial phase of iopromide (213 vs. 223; $p > 0.05$). Overall, vascular enhancement correlated well with perceived vascular conspicuity scores for both agents.

Conclusion: TaCZ provides both an absolute and relative contrast advantage compared to iopromide for improved visualization of the thoracic arteries and veins across a broad range of timepoints after contrast injection.

Clinical Relevance/Application:

TaCZ gives superior prolonged thoracic vascular enhancement over iodine agents at CT and warrants clinical testing as a means to improve the quality and consistency of CT angiograms and venograms.



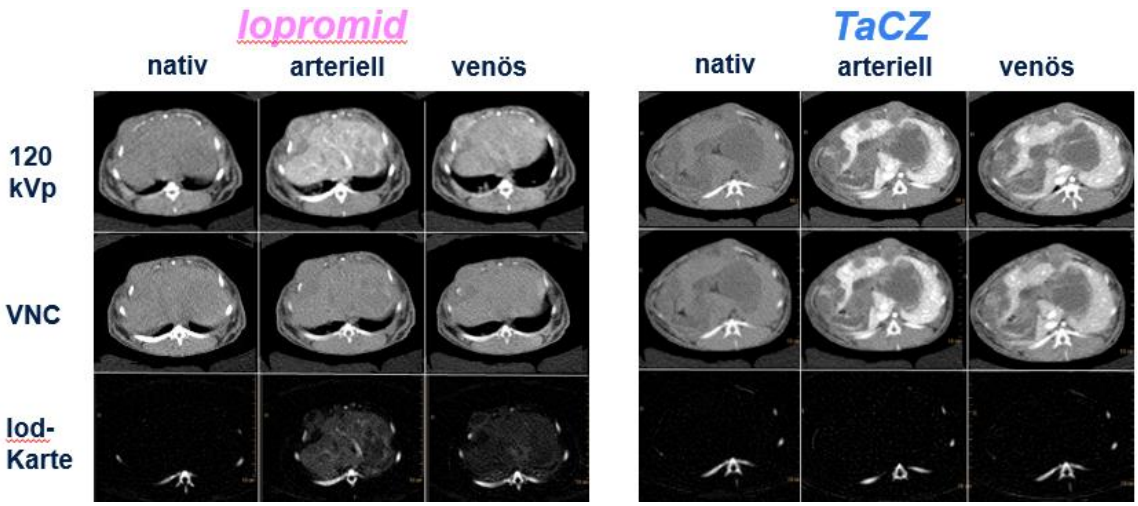
Heimer MM, **Sun Y**, Okwelogu N, **Bonitatibus PJ**, Meyer DE, Bales B, Houshmand S, **Yeh BM** "Benchmarking a Novel Intravascular Tantalum Oxide-based CT Contrast Agent in a Multiphase Protocol: Preliminary Results of a Preclinical Study" RöFo 2023, 195(S01), S43. DOI:10.1055/s-0043-1763058. Also presented at the German X-ray Congress; Wiesbaden, Germany; May 2023.

Zielsetzung: To compare the CT imaging performance of a novel intravenous carboxybetaine zwitterionic coated **tantalum** oxide (**TaCZ**) nanoparticle CT contrast agent with that of a conventional iodinated (iopamidol) contrast agent in a rabbit model.

Material und Methoden: Four rabbits were serially placed inside an adipose-equivalent encasement emulating normal abdominal girth of 102 cm and scanned on a Spectral CT scanner (Philips IQon, Best, Netherlands) at arterial and venous delays after intravenous injection of 540 mg element (Ta or I) per kilogram of body weight of **TaCZ** or iopamidol. For each time point, contrast enhancement of the aorta, portal and hepatic veins, as well as the liver parenchyma were measured in Hounsfield Units (HU) by placing circular regions of interest. Effective Z-numbers were also measured for the aorta and liver parenchyma. Findings were compared using a paired T-test for independent samples.

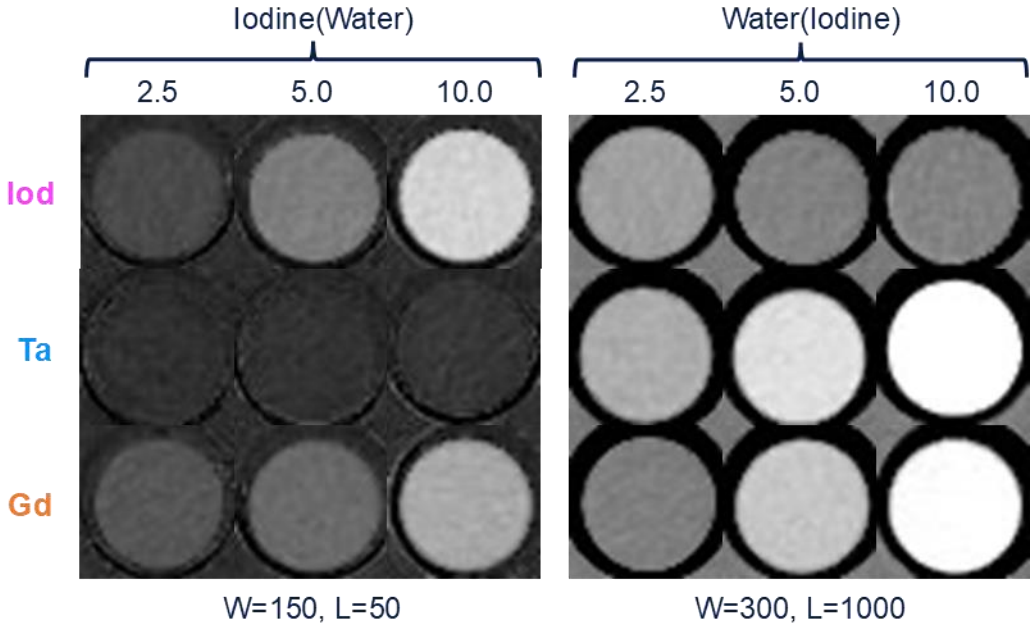
Ergebnisse: Mean peak enhancement for both arterial and venous phases were higher for **TaCZ** than for iopamidol in the aorta (365 vs. 264 HU p=0,62; and 227 vs. 142 HU p<0,001), portal vein (406 vs. 220 HU p=0,01; and 251 vs. 145 HU p=0,001), hepatic vein (227 vs. 168 HU p=0,34; and 257 vs. 145 HU p<0,001) and liver parenchyma (166 vs. 112 HU p=0,049; and 147 vs. 110 HU p=0,029). Effective-Z measurements were significantly lower in both the aorta (6,72 vs. 9,94 p=0,019; and 7,04 vs. 8,79 p<0,001) and liver parenchyma (7,01 vs. 8,24 p=0,002; and 7,07 vs. 8,14 p<0,001) after injection of **TaCZ** compared to iopamidol.

Schlussfolgerungen: An experimental **tantalum** nanoparticle–based intravenous contrast agent showed greater contrast enhancement compared with iopamidol at arterial and venous delay phases in a rabbit model; spectral decomposition algorithms allow differentiation of **tantalum** and iodine which indicates valuable applications for multi-energy CT imaging.



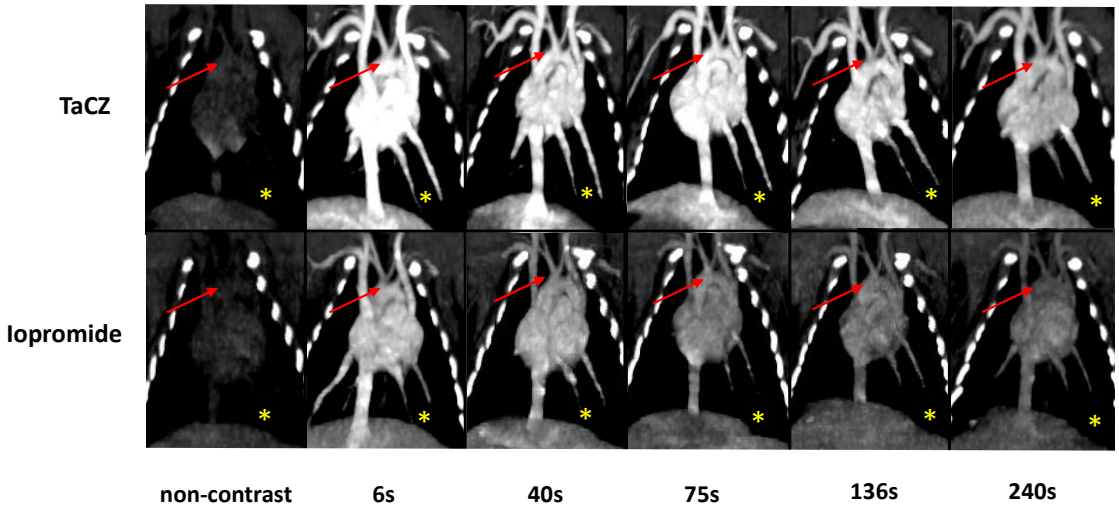
Sun Y, Heimer MM, Yin Z, Bales B, **Bonitatibus PJ**, **Yeh BM** "Evaluation of an Experimental Tantalum Oxide Contrast Material for Material Separation from Iodine and Gadolinium using DECT and PCCT" Radiological Society of North America (RSNA); Chicago, IL; November 2023.

Purpose: To evaluate material separation of an experimental **tantalum**-oxide nanoparticle contrast agent (TaCZ) from iodine and gadolinium, using clinical DECT and a prototype deep silicon PCCT scanner. **Materials and Methods**: Vials of the following concentrations of contrast agents: 2.5, 5.0, 10.0 mg iodine/mL (Ultravist, Bayer); 2.5, 4.0, 5.0, 12.0 mg Gd/mL (Multihance, Bracco); 2.0, 2.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 mg Ta/mL (TaCZ) were scanned in a water-equivalent CT phantom (MECT Phantom, Gammex) on a clinical fast-kV switching DECT scanner (Revolution CT, GE) and a prototype deep silicon PCCT. Paired iodine and water material decomposition (MD) images were generated for both scanners. Also, PCCT bin images were generated (bin A, 44–52 keV; bin B, 52–60 keV; and bin C, 60–80 keV). ROIs were drawn on 10 slices per vial for all image reconstructions to measure average CT attenuation, iodine and water signals. Slopes of iodine vs material concentration graphs were compared for MD images, and higher to lower bin CT number ratios were compared in the bin images.
Results: Slopes of iodine signal versus elemental concentration for DECT and PCCT are 1.06 and 0.93 for iodine; 0.38 and 0.02 for Gd; and 0.10 and -0.04 for Ta, respectively. For MD maps, a larger slope difference is seen for iodine vs Ta than for iodine vs Gd, suggesting better spectral separation of iodine from Ta by DECT and possibly PCCT. Separation of Ta from Gd appears modest ($\Delta = 0.28$) but poor for PCCT ($\Delta = 0.14$) because both materials are correctly classified as non-iodine by 2-MD. However, in PCCT bin images, Gd signal (K-edge 50.2 keV) is optimized between bins A & B with an attenuation ratio of ~1.38 between those bins, while Ta signal (K-edge 67.4 keV) is optimized between bins B & C with a ratio of ~1.26. Attenuation ratios of other materials, including iodine and water are all ≤ 1.0 for these same bin pairs, indicating promising bin-based material separation of Ta and Gd from iodine and other materials.
Conclusion: Iodine signal is more readily separated from that of Ta than Gd by DECT material decomposition images and is slightly more readily separated from that of Ta than Gd by PCCT. When using PCCT bin (non-MD) images, both Gd and Ta signals are readily differentiated from that of iodine, from each other, and from other materials.
Clinical Relevance: Experimental **TaCZ** contrast gives a strong "color" signal that should be readily separated from iodine signal by both DECT and PCCT, and from Gd for PCCT, and may enable future multi-color contrast discrimination.



Heimer MM, **Sun Y**, Grosu SR, Cyran CC, **Bonitatibus PJ**, Okwelogu N, Bales B, Meyer DE, **Yeh BM** "Novel Intravascular Tantalum Oxide-based CT Contrast Agent Achieves Improved Vascular Contrast Enhancement and Conspicuity Compared to Iopromide in an Animal Multiphase CT Protocol" Investigative Radiology 2024, Under Review.

Purpose: To assess temporal thoracic vascular contrast enhancement of a novel intravenous **tantalum** oxide (TaCZ) nanoparticle CT contrast agent compared to a conventional iodinated CT contrast agent (iopromide) in a rabbit multiphase CT protocol.
Materials and Methods: Five New Zealand White rabbits were scanned inside a human-torso-sized adipose-equivalent encasement on a clinical CT system (Philips IQon, Best, Netherlands) before and 6, 40, 75, 136, and 240 s after intravenous injection of 540 mg element (Ta or I) per kilogram of body weight of TaCZ or iopromide. Both contrast agents were assessed in a single session. Net contrast enhancement of various arteries and veins as well as image noise were measured. Randomized scan series were reviewed by three independent readers on a clinical PACS system and assessed for vascular conspicuity and image artifacts on 5-point Likert scales.
Results: Overall, vascular enhancement achieved with TaCZ was superior to iopromide in all examined thoracic vessels and at all time points (all; $p < 0.05$), except for the inferior vena cava (IVC) at 6 s ($p = 0.132$); achieved contrast enhancement was highest for TaCZ at 6 s (296.3 ± 21.4 HU) and lowest for iopromide at 240s (49.3 ± 10.9 HU). Overall, achieved arterial contrast enhancements of TaCZ at delays of 6, 40, and 75 s were superior to optimum achieved iopromide contrast enhancement (all; $p < 0.05$, except IVC at 6s). Vascular conspicuity achieved with TaCZ was superior compared to iopromide at all time points (all; $p < 0.05$), with substantial inter-reader reliability ($\kappa = 0.61$; $p < 0.001$) and strong positive monotonic correlation between subjective conspicuity scores and objective measurements ($\rho = 0.828$; $p < 0.001$).
Conclusion: TaCZ provides absolute and relative contrast advantage compared to iopromide for improved visualization of thoracic arteries and veins in a multiphase CT protocol.



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