Contrast Media
History and Chemical Properties

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KEYWORDS

• Contrast media • Cardiac catheterization • History

KEY POINTS

- Contrast media, which are essential for cardiac catheterization, are classified based on water solubility and osmolality.
- Contrast media were discovered during the search for a treatment of syphilis, and initial agents were developed in urology.
- Contrast media agents have evolved from high-osmolar agents with many side effects to low-osmolar and iso-osmolar agents with considerably fewer side effects to the patient.

INTRODUCTION

Since the time of Hippocrates, physicians have sought better tools to diagnose disease. Röntgen's discovery of x-rays enabled physicians to use this modality in improving diagnosis of disease in patients. Radiology has rapidly evolved, and the improvement has partly been successful thanks to different types of contrast media that have been invented to better visualize tissues.

Cardiac catheterization uses x-rays and contrast agents to visualize the heart. Contrast agents are essential for imaging the cardiac chambers and coronary vessels, and the evolution of contrast agents has had a significant effect on cardiology.

This article reviews the classification of contrast agents, a brief history of development of contrast agents, and the chemical properties of agents currently used in cardiac catheterization.

CLASSIFICATION OF CONTRAST AGENTS

All contrast media used in cardiology are distributed intravascularly and extracellularly. They are classified into ionic and nonionic groups based on water solubility. Ionic agents are water soluble, as they dissociate into negative and positive ions. These ions then bind with the negative and positive poles of water molecules. Nonionic agents do not dissociate but are water soluble because of their polar OH groups.[1]

Contrast agents are further divided based on their osmolality into high-osmolar contrast media (HOCM), low-osmolar contrast media (LOCM), and iso-osmolar contrast media (IOCM). **Box 1** lists some of the most common contrast agents sorted by class. Contrast agent ratio is used to further classify contrast media; this ratio is calculated by the number of iodine atoms divided by the number of particles in solution. **Table 1** shows the differences in osmolality and contrast agent ratios for some contrast media. Iodine content in relation to osmotic particles per molecule is the most important factor impacting attenuation.[1,2]

All contrast agents have a basic structure of a benzene ring, which is composed of 6 joined carbon atoms, each of which has an attached

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Box 1
Classification of contrast media

Ionic media

- Monomers: high-osmolar contrast media
  - Examples: ioxithalamic acids, diatrizoate
- Dimers: low-osmolar contrast media
  - Example: ioxaglate

Nonionic media

- Monomers: low-osmolar contrast media
  - Examples: iohexol, iopamidol, ioversol, iopromide
- Dimers: iso-osmolar contrast media
  - Examples: iodixanol, iotrolan

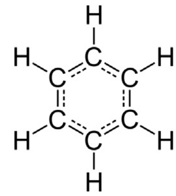

Fig. 1. A benzene ring is composed of 6 joined carbon atoms, each of which has an attached hydrogen atom. Dashed lines represent delocalization of electrons over the carbon atoms. C, carbon atom; H, hydrogen atom.

hydrogen atom (Fig. 1). Contrast media consist of triiodinated benzene rings, whereby 3 hydrogen atoms are replaced with attached iodine atoms. Monomers contain 1 triiodinated benzene ring, and dimers contain 2 triiodinated benzene rings. Attachment at the first carbon atom differentiates ionic from nonionic contrast agents, with sodium or another cation, such as meglumine, attached in ionic agents and an amide group attached in nonionic agents. The iodine molecule is attached at carbon atoms 2, 4, and 6. Iodine has a tight bond to the carbon atoms, which augments attenuation by increasing the linear coefficient of radiation. Side chains containing OH groups are attached at carbon atoms 1, 3, and 5 and functions to raise solubility and decrease protein binding.

HISTORY OF IMAGING

In 1895, at The University of Wurzburg, Wilhelm Conrad Röntgen discovered x-ray by passing electrical charges through vacuum tubes. The letter x was used, as it was the mathematical term to designate an unknown variable.[3] Within a month after Röntgen's discovery, x-rays began to be used for medical purposes.[4] However, initial x-rays were low power and made visualization difficult. By 1896, more than 1000 papers had been published on x-rays, including 500 publications on x-rays used for medical applications.[5]

X-rays were quickly found to have limitations and required enhancement to produce better images. Haschek and Lindenthal in Vienna discovered that bismuth, lead, and elements with high atomic numbers enhanced x-ray images but were not safe for use in humans.[6] Therefore, the search for optimal, safe contrast agents continued.

Advancements in imaging were first made in imaging of the urinary tract. In 1897, Hurry Fenwick used x-rays to detect kidney stones before urologic surgery.[7,8] He then introduced bougies infused with metal into the ureters, enabling the visualization of the course of the ureters and localization of calculi with x-ray imaging.[4]

To further improve visualization with x-rays, a radiopaque agent administration was necessary. In 1906, Von Lichtenberg and Voelcker used an agent to create retrograde pyelographic studies.[9] They initially used a 2% colloidal silver solution. However, this was found to be toxic to the kidneys, at times even resulting in death.

Table 1
Iodinated contrast media

Classification	Iodine Atoms per Molecule	Osmotic Particles per Molecule	Contrast Agent Ratio	Molecular Weight	Osmolality (Osm/kg Water)
Ionic monomer	3	2	1.5	600–800	1.5–1.7
Nonionic monomer	3	1	3	600–800	0.6–0.7
Ionic dimer	6	2	3	1269	0.56
Nonionic dimer	6	1	6	1550–1626	0.3

Data from Aspelin P, Bellin MF, Jacobsen JA, et al. Classification and terminology. In: Thomsen HS, editor. Contrast media - safety issues and ESUR guidelines. 2nd edition. New York: Springer; 2009. p. 1–4; and Dawson P, Cosgrove DO, Grainger RG, editors. Textbook of contrast media. Oxford (United Kingdom): Isis Medical Media Ltd; 1999.