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Pressure injectors for radiologists: A review and what is new

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Abstract

Pressure Injectors are used routinely in diagnostic and interventional radiology. Advances in medical science and technology have made it is imperative for both diagnostic as well as interventional radiologists to have a thorough understanding of the various aspects of pressure injectors. Further, as many radiologists may not be fully conversant with injections into ports, central lines and PICCs, it is important to familiarize oneself with the same. It is also important to follow stringent operating protocols during the use of pressure injectors to prevent complications such as contrast extravastion, sepsis and air embolism. This article aims to update existing knowledge base in this respect.

Key words: Connectors; Poiseuille's law; power PICC; pressure injectors; tubings

Introduction

Pressure injectors and dry imaging cameras are routinely used accessories in interventional radiology, computed tomography (CT) and magnetic resonance imaging (MRI). In radiology practice, our knowledge of pressure injectors and dry imaging cameras is largely superficial and overwhelmed by more exhaustive operational data of clinical modalities. To fulfil this academic void on the two neglected topics, dry imaging camera was dealt with earlier in this journal[1] and the spotlight now moves on to pressure injectors.

The functioning of a pressure injector involves a blend of concurrent processes in areas of diverse sciences like computers, pressure, thermal, electricity, battery operations, non-ferromagnetic metallurgy, rheology, viscosity, syringe and catheter technologies.

Pressure injectors or power injectors in imaging and interventional radiology ensure optimized opacification and delineation of normal anatomy, including arterial and venous anatomy and abnormal lesions. Today, several imaging and interventional studies require pressure injectors, as in CT (CT angiography, three-phase abdominal organ studies, cardiac CT, pre- and post-stent analysis, and perfusion CT and MRI [contrast-enhanced MR angiography (MRA), cardiac MRI, and perfusion MRI]. This review article provides an overview of pressure injectors and pressure injection in radiology practice in different modalities.

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Basic physics of pressure injection

At its very core, the concept of using pressure injection in vascular channels is governed by Poiseuille's law. Poiseuille's law interprets that a laminar flow through a cylindrical pipe varies inversely with the viscosity of the medium and the length of the tube and directly with the pressure difference across the tube and the fourth power of the radius of the tube.[2]

A common unit for pressure used by manufacturers of medical devices is psi. It denotes pounds per square inch and is a unit of pressure or of stress. It is the pressure resulting from a force of one pound applied to an area of one square inch. Pascal is a new unit and 1 psi is approximately 6894.757 Pa.[3]

Components of a pressure injector

In their construction, pressure injectors or power injectors consist of an injector "head" where syringes with contrast material are inserted, piston plungers that deliver the contrast from the syringes, and pressure tubing that connects the syringe and vascular system of the patient.[4]

- The piston plunger has a plunger drive ram, a drive motor that moves the drive ram, an elastic head, a stretcher rod, and a syringe [Figure 1]. Functionally, these four parts are in sequential contact starting with the drive ram. The elastic head can either expand or contract as the drive ram advances or retracts against or from the stretcher rod
- Pressure syringes are transparent, latex free, and provide a crystal-clear view of the contrast medium. Syringes are pre-filled or manually loaded. The injector system may be single (for contrast only) or dual syringe (for contrast and saline). Filling options of the syringes by J-tube or spike filling are required when manual loading is done [Figure 2]
- Most displays are located encasing the injector head. They have user-defined protocols to inject with variables of phase, rate, delay, and volume. Color pressure sensitive touch screen enables different colors for operations like loading, arming, and injecting
- Pressure tubing and connectors are needed to transmit the selected amount, pressure, flow, and rate of contrast accurately, between the injector system and the patient, particularly during concurrent scanning and table movement.

Operational features of pressure injector

The salient features of pressure injectors are given in Table 1. Operation factors to be considered are the concentration and volume of contrast material; the phases, rate, and duration of the injection; whether or not a saline flush is used [Figure 3]; the timing delay between contrast injection and initiation of scanning; and adjustments for variations in patient's cardiac output.[5]

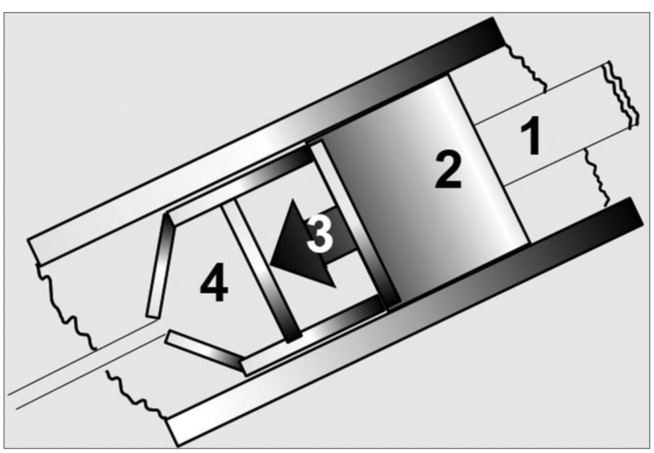

Figure 1: Line diagram of piston plunger in pressure injector system: Piston plungers are made of (1) plunger drive ram, (2) drive motor for moving the drive ram, (3) elastic head and a stretcher rod and (4) syringe. Importantly the four parts of pressure head are in sequential contact

Pressure injectors have been developed for different modalities in radiology [Figures 4-6]. The important differences in their functioning at dedicated locations within radiology departments are summarized in Table 2.

Table 3 depicts the different pressure injectors manufactured by vendors since the last few years. It additionally displays the chronology of mergers and acquisition of vendors and their products.

Table 1: Salient features of pressure injectors

Component	Parameter	Features
Configuration	Mounting	Table/pedestal (wheels)/wall/ceiling
	Weight	Up to 20 kg
Power head	Phases	Single/multiple up to six phases
	Pressure	Low-pressure/high-pressure operation
	Head	Single head/dual head
Operations	Operations	Start/stop injection inside/outside suite
	Programmable	Establish, select, modify phasic user-defined protocols
	Protocol memory	Up to 100 injection protocols
	Mode switching	Switch from injection mode to drip mode Switch between cardio, angio, and CT modes
	Tilt facility and warning	Tiltability Inject button activated after tilted downward
Display	Display	Full color/black and white Touch screen
	Display orientation	Horizontal/vertical/rotation
Syringe	Material	Clarified polypropylene
	Size	10-200 ml depending on modality
	Flow knob	Manual/automatic
	Sterilization	Epoxy ethane/asepsis and its validity duration

CT: Computed tomography

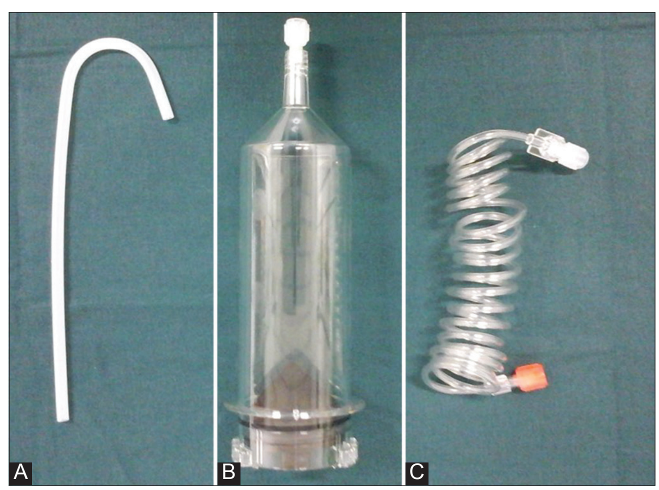

Figure 2 (A-C): Functional components of syringes in pressure injector system (left to right) (A) syringe filling option is by J-tube or spike filling (B) pressure syringes are latex free, transparent, either pre-filled syringes or manually loaded and (C) pressure tubing and connectors transmit selected amount, pressure, flow and rate of contrast accurately, between the injector system and the patient, particularly during concurrent scanning and table movement

Few operational issues in pressure injector

- Multiphasic study: The advantage of the biphasic injection is that it can optimize and prolong contrast enhancement. An alternative, yet effective approach is an exponentially decelerated injection rate over time[5]
- Timing bolus: A timing bolus injection of contrast medium followed by a saline flush is performed occasionally to determine the ideal scan delay for optimum image quality[18]
- **Saline chaser:** The use of a saline flush immediately following contrast injection has several potential advantages. Typically, a double-barrel power injector is required for a saline flush. It pushes the contrast material into the vascular system of the patient that would otherwise be left behind in tubing. It assists antegrade movement of contrast bolus, which facilitates an optimal bolus shape. The amount of contrast in image acquisition is marginally increased and recent studies show that it reduces thoracic venous artifacts.[19] It clears the vascular access site of residual contrast after injection[5]

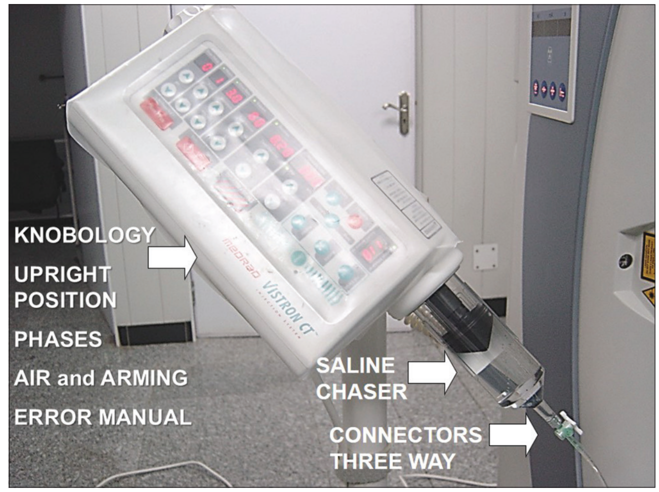

Figure 3 (A-E): Basic operational issues in pressure injectors (Medrad Vistron CT) include (A) working knowledge of phases, volume, rate, delay (B) an upright position during injection (C) arming after removal of air (D) a saline chaser that offers several advantages and (E) a correct handling of connectors and three way

Table 2: Pressure injectors and modalities

Parameter	Angiography/DSA	CT	MRI
Sizes of pre-filled syringes	50, 75, 100, 125, 150 ml	100, 125, 130, 200 ml	10, 15, 20, 30, 60, 65, 110 ml
Pressure limit (psi)*	75-1200 psi	75-300 psi	150 psi
Flow rate ml/sec	0.1-50.0	0.1-10.0	0.1-10.0
Inject/scan delay (s)	0-300 s	0-500 s	0-60 s
Power	AC powered	AC powered	Battery operation DC powered usually
Non-ferromagnetic compatibility	-	-	1 T/1.5 T/3 T compatibility

*Pressure rating of catheters is different from pressure limiter of pressure injectors.[6]
MRI: Magnetic resonance imaging, CT: Computed tomography, DSA: Digital subtraction angiography

Table 3: Pressure injectors and vendors

Vendor	Alliance partner	Angiography/DSA	CT	MRI
Bayer health care[7,8]	1995: Medrad acquired by Schering AG 2006: Schering AG acquired by Bayer AG[9]	MK II, MK III, MK IV Mark 7 Arterion Avanta	Envision CT Vistron CT Medrad 200 MKIV/CT MCT/MCT Plus MKV/MKV Plus MKV ProVis® Stellant Sx Stellant D Stellant D dual flow	Spectris Spectris solaris MR Spectris solaris EP
Bracco[10]	2001: Bracco merges with Acist[11]	ACISTCVi	Empower CTA Double barrel ACIST Empower	Empower MR EZEM MRI
Covidien[12]	1981: Mallinckrodt listed among Fortune 500 1996: Mallinckrodt acquires Liebel-Flarsheim 2000: Tyco acquires Mallinckrodt 2007: Tyco becomes Covidien 2011: Schiller India ties with Covidien[13] 2013: Covidien and Mallinckrodt officially separated[14]	Angiomat 3000 Angiomat 6000 Angiomat Illumena (DSA/CT)	OptiStat Angiomat 9000 CT 9000 ADV CT Optivantage DH	Optistar MR Optistar LE Optistar Elite
Medtron[15]		Accutron HP Accutron HP-D	Accutron CT Accutron CT-D	Accutron MR
Nemoto Kyorindo Co Ltd[16]	GE Nemoto alliance in 1996-1997 onward	Press Duo Press Pro	CT dual-shot NCOM CT dual-shot GX7 A 800 A60	Sonic shot GX
Ulrich[17]		-	Ohio tandem Missouri	Ohio M Tennessee Mississippi

MRI: Magnetic resonance imaging, CT: Computed tomography, DSA: Digital subtraction angiography

- Warmer/heater: An inverse relationship exists between viscosity and temperature in liquids. An increase in temperature of the contrast medium results in a concomitant decrease in its viscosity.[20] Consequently, warmed contrast media are less viscous and offer lesser resistance.[18] Flow rate improvement occurs only when using high-viscosity contrast media through 4-5 F catheters. Flow rate improvement is not evident while warming lower-viscosity contrast and with larger catheters.[2] In general, extrinsic warming of iodinated contrast material to body temperature minimizes the complications for high-rate (>5 ml/s) intravenous low osmolar injections, injections of viscous iodinated contrast (e.g. iopamidol 370, Bracco Diagnostics Inc, New Jersey, USA),[21] direct arterial injections through small-caliber catheters (5 F or less), and intravenously injected arterial studies in which timing and peak enhancement are critical features[20]

  Conversely, extrinsic warming of iodinated contrast material may not be beneficial for low-rate (≤5 ml/s) intravenous low-osmolar power or hand injections, injections of low-viscosity contrast media, direct arterial injections through large-bore catheters (6 F or more), and intravenous injections in which peak opacification and timing are not critical
- Prefilled disposable syringes: Prefilled syringes offer numerous advantages such as lesser medication errors, reduction in the risk of infection, and improved efficiency.[18] By avoiding filling and refilling, prefilled syringes reduce the risk of microbiologic contamination.[22]

Patient issues in pressure injection

- Common intravenous routes: The preferred venous access site for pressure injection is peripheral intravenous, usually in antecubital or large forearm vein. A fundamentally important step in pressure injection is to ensure that the catheter lies within the venous system. Such an intravascular placement is indicated firstly by a low-resistance saline flushing of the line and secondly by successful aspiration of blood with backflow from the line.[6] As regards foot veins, power injection for all sizes can be performed if there is no other intravenous access. However, contrast is recommended to be injected at foot veins at 1 ml/s within 100 psi. Three-phase exams should not be performed using intravenous access in hand veins or lower extremity[23]
- Other intravenous routes: They include peripherally inserted central catheters (PICCs), chest ports, central lines, and intravenous cannulas inserted into internal or external jugular vein.[28] Pressure injection of contrast media through central venous catheters for CT examinations is feasible and safe when the set hospital guidelines and injection protocols are followed.[29] Devices specifically designed for power injection are generally rated for pressures of 300 psi and flow rates of up to 10 ml/s.[6] Notwithstanding this, the vendor product sheet of all devices should be meticulously scrutinized before its use in pressure injection. An overview is displayed in Table 4
- Pediatric cases: Issues unique to administration of intravenous contrast to neonates and children comprise use of shorter catheters, smaller volumes

Table 4: Contrast injection in peripheral intravenous routes, catheters, and lines[20,23-26]

Route/catheters and lines	Specific route	Pressure/hand injection	Gauge	Max (psi)	Max flow rate adult (ml/s)	Max flow rate pediatric (ml/s)
Peripheral intravenous	Peripheral intravenous at antecubital vein	Pressure or hand	18 G		6	2
		Pressure or hand	20 G		3[20]	2
		Pressure or hand	22 G		5[20]	2
		Hand injection only[23]	22 G			
		Hand injection preferred Pressure with caution	24 G[24]	150	Not greater than 1.5	1.5
	Peripheral intravenous at wrist or hand[20]	Hand injection preferred Pressure with caution	22 G		Not greater than 1.5	
	Peripheral intravenous at foot lines[23]	Hand injection preferred Pressure with caution		100	1	
	Peripheral intravenous at groin lines[23]	Hand injection only				
	Scalp vein sets	Hand injection only				
Conventional peripherally inserted central catheters	Conventional PICC	Hand injection only		25		
	Conventional central lines in adults[20]	Hand injection preferred Pressure injection in large bore	Large bore 9.5-10 F		2.5	
	Conventional central lines in children[2]	Hand injection preferred Pressure injection with caution		25	0.5-2	
	Angiocatheters*inserted into EJV[23]	Pressure or hand injection		150	2	
PowerPICC	Purple PICC[27]	Pressure		300	5	

*Hand injection only: Angiocatheters inserted into internal jugular vein IJV, chest ports, ports in pediatric patients, and conventional Hickman catheter.[23] *Unacceptable for any IV contrast: Swan-Ganz, Mediport, Groshon, dialysis catheters.[23] PICC: Peripherally inserted central catheters of contrast, slower injection rates, smaller gauge (24 G) angiocatheters, and unusual vascular access sites. A study of 554 children subjected to a power injector revealed the incidence rate of extravasation to be 0.3%.[24]

Safety issues in pressure injection

Standard operating procedures should be used in pressure injection to minimize the two big risks, namely risk of contrast extravasation and air embolism.

- Extravasation: The reported incidence of intravenous contrast media extravasation related to power injection for CT ranges from 0.1 to 0.9%.[20] Factors associated with higher extravasation rate include high flow rates with low-diameter intravenous catheters (22 G) and location of intravenous catheter in hand.[30] Any extravasation incident is documented with a checklist containing volume and type of the contrast extravasated, gauge of intravenous access, location of intravenous catheter, the person who started the intravenous access, the person who monitored the injection, rate of injection, the radiologist and nurse who were notified of the extravasation, and the level of pain expressed by the patient (mild, moderate, or severe).[23] Treatment options include elevation of affected extremity, use of cold compresses, aspirating the extravasated contrast, or local injection of corticosteroids or hyaluronidase[20]
  Preparation of the pressure injector system is the key to minimize the risk of extravasation or air embolism. To meet this requirement stringently, every department should have a standard operating procedure at the beginning of a working day and for each case. Salient points in the standard operating protocol (SOP) include: (a) clearing the syringe and pressure tubing of air; (b) reorienting the syringe with the tubing directed downward; (c) checking the position of catheter tip for venous backflow (if backflow is not obtained, a saline test flush or special monitoring of site during injection may be needed);[20] (d) if the venipuncture site is tender or infiltrated, an alternative site is acquired; (e) enough play on the intravenous line, tubing, and pressure injector system should be permissible during concurrent table movement; and (e) good two-way communication with the patient should be established in each case
  From our personal experience of handling pressure injectors of different modalities, the right antecubital vein is preferred in CTA evaluation of aortic arch aneurysms. Thoracic aortic aneurysms at the left may cause obstruction of left brachiocephalic vein, redirecting the venous blood into the accessory hemiazygos and azygos venous system [Figure 7A-D]. Potential blockage at the left brachiocephalic vein is predicted by recognizing one of the two subtle signs: In this case, by the absence of backflow of blood out of venflon cannulation and the presence of a free unobstructed flow of saline
- Air embolus: Clinically, large amount of air in the venous system results in various effects such as dyspnea, cough, chest pain, pulmonary edema,

Figure 4 (A-C): Angiography / DSA Pressure Injectors (Liebel-Flarsheim). Few functional issues include (A) light, manoeuvrable and small footprint (B) protocols with variables of phase, volume, rate and delay (C) wide range of injection rates upto 45 ml/sec for aorta

Figure 5 (A-C) : CT Pressure Injectors: (Covidien CT OptiVantage DH) Functional issues in newer CT pressure injectors include (A) programmable user defined protocols (B) colour pressure sensitive touchscreen that offers different colours for operations like loading, arming, injecting (C) availability of vendor specific sensors such as RFID-enabled syringes/power injectors, and syringe volume sensors

Figure 6: MR pressure injectors (Medrad Spectris). Functional issues include (A) battery operations (12 V DC, 25 A) which charges at console, discharges at MRI suite (B) non-ferromagnetic status and (C) availability of vendor specific sensors such as keep vein open for intermittent injection

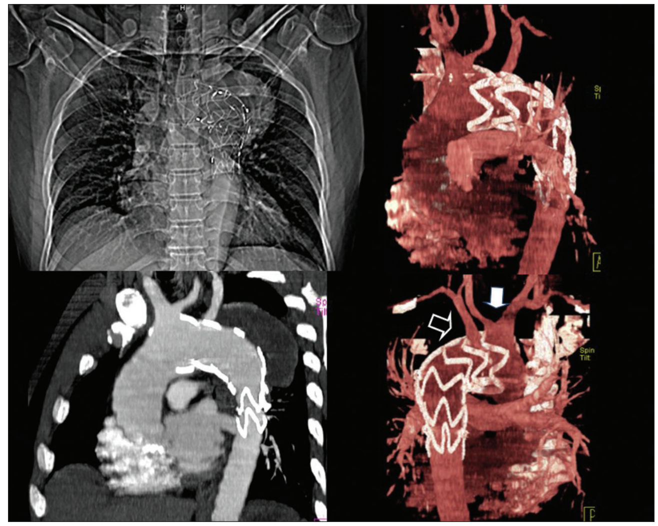

Figure 7 (A) : Potential hazard in pressure injection. Initial post stenting follow-up injected via right antecubital vein shows large, lobulated stented aortic arch aneurysm. Oblique MPR shows stent integrity with no endoleak. 3DVR displays stent *in situ*, a common origin of Lt CCA and BCA (white arrow), and LSCA take off through uncovered portion of stent (open arrow)

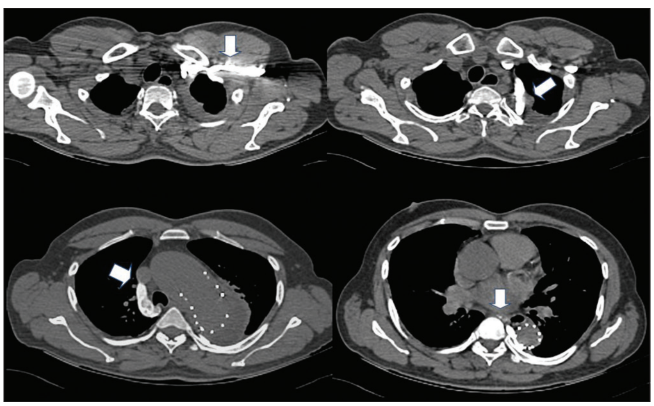

Figure 7 (B): Second follow-up study via left antecubital vein. This was an aborted study due to extravasation. Axial CECT (open arrows) shows opacification of left axillary, subclavian vein, accessory hemiazygos vein and azygos. Opacified accessory hemiazygos vein descends in a left paravertebral course and a prevertebral cross over to right at T5 to T9 to join the azygos

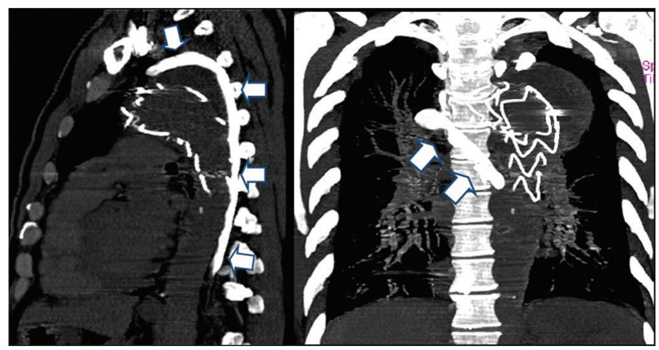

Figure 7 (C): 3D Sagittal MIP shows opacified accessory hemiazygos vein, its descending course (open arrows) paravertebrally behind the stented thoracic anueurysm; 3D Coronal MIP shows the prevertebral crossover from T5 to T9 (open arrows), where it joins the azygos vein

tachycardia, hypotension, and deficits like stroke. Patients with right-to-left intracardiac shunts or pulmonary arteriovenous malformations are at a higher risk of having a neurological deficit developing from small volumes of air embolism.[20] On CT, venous air embolism is identified as air bubbles/air-fluid levels in the intrathoracic veins, main pulmonary artery, and right ventricle, and occasionally in the intracranial venous structures.[31] Treatment includes administration of 100% oxygen and placing the patient in left lateral decubitus position[20]

- *Sepsis:* Using aseptic technique during loading/emptying the left over contrast and/or saline, preferred use of pre-filled syringes, and hand hygiene can prevent sepsis. In a study, double-syringe injectors used with disposable or prefilled contrast agent syringes ensured hygienic conditions in routine clinical practice. The organisms evaluated in this study were coagulase-negative staphylococci, micrococcus, and bacillus species.[22] Changing the pressure syringe/tubing system is mandatory when it is accidentally contaminated with blood
- Off-label pressure injector usage of gadolinium: Off-label is a term used to describe the use of contrast media for a clinical indication that is not contained in the manufacturer's labeling.[20] While hand injection of gadolinium is approved in the United States by the Food and Drug Administration (FDA), gadolinium chelate is not yet approved for use in a pressure injector.[20] Even though such usage is not approved by the FDA, radiologists occasionally use gadolinium off-label depending on a justifiable clinical need, as in contrast

enhanced Magnetic resonance angiography (CEMRA), perfusion MR, and cardiac MR

- *Safety reminders from the FDA:* Ruptured vascular access devices from use of power injection in CT/MRI studies is featured in over 250 adverse event reports with FDA that are spread over several years. Simply put, adverse events occur despite there being reports in the literature, letters from manufacturers, and warnings in power injector's labeling.[32] The ruptured devices resulted in fragmentation, embolization or migration, extravasation, loss of venous access requiring device replacement, and contamination with blood and contrast media.[32]

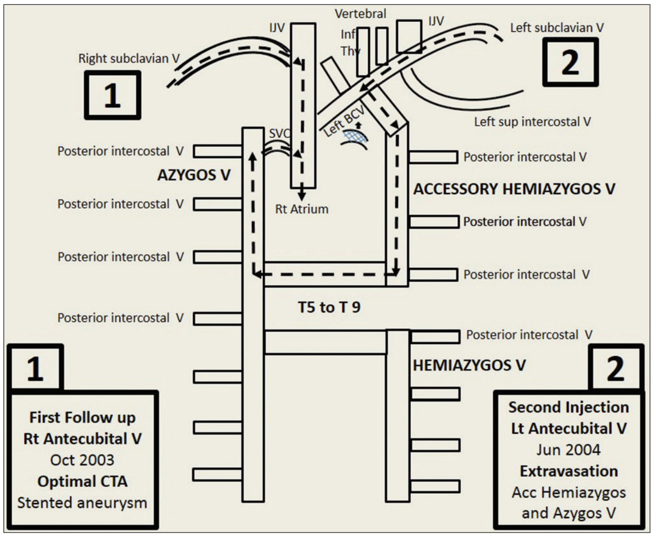

Figure 7 (D): At left is initial follow up CTA in Oct 2003 using a right antecubital vein displaying stented aneurysm; At right is follow up CTA in Jun 2004 using a left antecubital vein injection aborted due to an extravasation, predicted by absent free backflow in venflow. The alternate pathway was by accessory hemiazygos and azygos vein, probably a re-routing due to thoracic arch aortic aneurysm blocking the left brachiocephalic vein

Recent advances in pressure injectors/pressure injection

- Sensors: Different types of sensors are available across pressure injector systems of vendors [Table 5]
- Dual flow: Dual flow is a new feature available in Medrad Stellant D, MEDRAD Inc, Warrendale, USA pressure injectors, wherein contrast and saline can be injected at the same time. The simultaneous injection in dual flow enables variable amounts of contrast and saline syringes that uniformly enhance left and right heart ventricles for ideal image quality, as well as optimally visualize right coronary arteries and right ventricle[33]
- Syringeless pressure injectors: CT Exprès (Bracco Engineering, Lausanne, Switzerland) is a syringeless releasing device for the delivery of contrast.[34] It permits simultaneous loading of two bottles, which facilitates multiple contrast-enhanced CT (CECT) scans without the need for contrast reloading. Syringeless systems allow higher contrast (1000 ml) and saline loading capacity during initial setup, which allows 8-15 CECT scans
- CT injectable PICC (PowerPICCs): It is estimated that by 2017, 95% of PICC devices sold in the United States will be power-injectable.[35] Conventional PICCs are

Table 5: Sensors in pressure injectors[3,7,8,10,12,14,16,18,33]

Vendor	Equipment	Model	Sensor	Function
Bayer health care	CT	Medrad stellant	XDS extravasation detector technology	Radiofrequency signal directly detects presence of extravasation and stops injection
	CT	Medrad Stellant	Automatic plunger sensing system	Detects and reacts to syringe state: Pre-loaded, empty, or removed
	CT	Medrad stellant SX	FluiDots	Quick detection of presence of fluid
	CT	Medrad stellant D	Auto syringe sensing	Auto load, auto retract, auto prime, and auto syringe sensing
	MRI	Medrad spectrum solaris	KVO keep-vein-open	Prevents vascular occlusions during injection intermissions
Bracco	CT	Empower CTA	Tilt sensor	Reduces the risk of air embolisms
	CT	Empower CTA	Voice prompts	Provides operational status and alerts
	CT	E-Z-EM™ Empower CT®	EDA extravasation detection technology	Measures electrical variances in skin surface occurring in extravasation
Covidien	DSA/CT	Angiomat Illumena	ADAWS air detection warning system	Detects air bubble and empty syringes
	CT	Opti Bolus DH CT 9000ADV	Opti bolus™	Bolus shaping software for controlled flow rate/volume ensures enhanced diagnostic images
	CT	CT Opti vantage DH	RFID syringes/power injectors	Transmits data between syringes and power injectors; prevents reuse of used syringe
	MRI	Optistar LE	Auto syringe detection	Detects syringe size
	MRI	Optistar elite	Patency check	Determines IV integrity by injection of small volume of saline
Nemoto Kyorindo Co Ltd	CT	Nemoto CT dual-shot	Real-time needle tip pressure monitoring	Monitors needle tip pressure and injection parameters
	CT	Nemoto CT	Leak detection support system	Detects contrast leaks with infrared rays

MRI: Magnetic resonance imaging, CT: Computed tomography

designed to tolerate pressures of 25-40 psi and are not designed to withstand the high pressures of power injection. PowerPICC catheters are specially designed to tolerate the high pressures set to a maximum of 300 psi. PowerPICC catheters are purple colored and labeled to differentiate them from conventional PICCs.[36] These purple PICCs are available in single-, dual-, and triple-lumen configurations
- Power source and MR pressure injectors: Traditionally, MR pressure injectors are battery operated due to the inherent DC nature of electrical supply within an MRI suite. In recent times, AC-powered MR injectors like Optistar LE, Covidien, Massachusetts, USA injector have emerged. Also, Empower MR, Wolverson, West Midlands, UK does not require batteries, since it uniquely utilizes a hydraulic mechanism[37]
- IT-enabled pressure injectors: IT-enabled pressure injector systems with dedicated hardware and software directly pull the work list and patient data from RIS, PACS, and HIS. They can store up to 500 injection protocols of different modalities. They are advantageous as they can ensure consistency in handling same and different patients for similar indications and for regions of examination.[38] Examples of such a system are Medrad's Personalized Patient Protocol Technology, MEDRAD Inc, Warrendale, USA (P3T®) and Nemoto's CE Evidence, Nemoto Kyorindo co. Ltd, Tokyo, Japan.[39]

Conclusion

Pressure injectors or power injectors are important accessories in modern radiology departments and are used in CT, MR, and Interventional Radiology suites. Amongst the important issues related to pressure injection are patient safety and pressure injections across central venous catheters. While their functioning and operational parameters have been established to a large extent, one, however, needs to understand the ongoing technical refinements across multiple vendors. The purpose of this review article fulfils a single point availability of current facts, concerning these diverse objectives.

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