Impact of Disruptions in the Tc-99m Supply Chain on Cardiac Testing

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Disability Adjusted Life-Years Lost due to Cardiovascular Disease per 100,000

- <900
- 900-1650
- 1650-2300
- 2300-3000
- 3000-3700
- 3700-4400
- 4400-5100
- 5100-5800
- 5800-6500
- >7900

Temporal Trends in US Mortality

Mortality (per 100,000) vs. Year

- All causes
- % Cardiac
- % Cancer

National Vital Statistics System. Centers for Disease Control
Steady Advancements in Cardiovascular Care

1958: Coronary arteriography developed (Sones)
1961: Risk factors defined
1962: First beta-blocker developed (Black)
1969: First description of CABG (Favaloro)
1972: NHBPEP
1976: First HMG CoA reductase inhibitor described (Endo)
1980: First implantable cardioverter-defibrillator developed (Mirowski)
1979: Coronary angioplasty developed (Grüntzig)
1983: CASS
1985: TIMI 1
1985: NCEP
1986: GISSI and ISIS-2
1992: SAVE
1993: Superiority of primary PCI vs. fibrinolysis in acute MI noted
2000: ALLHAT
2001: Benefit of cardiac resynchronization therapy in heart failure demonstrated
2002: Efficacy of drug-eluting vs. bare-metal stents determined
2009: Left-ventricular assist device as destination therapy in advanced heart failure shown to be effective
2009: Genomewide association in early-onset MI described
2009: Deep gene sequencing for responsiveness to cardiovascular drugs performed

History and Physical Exam are Limited

- Sensitivity: 90%
- Specificity: 63%
- PPV: 82%
- NPV: 77%
- Accuracy: 80%

N=168

Mild stenoses may result in perfusion defects without any other abnormalities. These can be detected by a variety of imaging modalities, although nuclear methods (shown) are most common.

Shift from oxidative metabolism results in increased glucose utilization and lactate production. Increased adenosine levels may lead to adaptive responses. These are only detectible using invasive methods or with investigational imaging methods such as magnetic resonance spectroscopy.

Impairments in diastolic relaxation occur before systolic dysfunction and can be detected with echocardiography (shown) and cardiac MRI. The use of these tools in stress testing remains investigational.

Regional and global systolic abnormalities can be detected with a variety of techniques including echocardiography (shown), nuclear methods and cardiac MRI.

EKG monitoring may reveal ST-segment depression or elevation depending on the severity of ischemia. This is a routine part of most stress testing modalities.

Symptoms are a relatively late finding in the ischemic cascade. The occurrence of chest pain during stress testing may be a helpful adjunct, but is neither sensitive nor specific on its own.

Untreated ischemia may lead to myocardial infarction shown here as an area of late gadolinium enhancement on cardiac MRI.
Approaches to Stress Testing
Single Photon Perfusion Tracers

99mTc-Sestamibi

99mTc-Tetrofosmin
Utilization of SPECT Myocardial Perfusion Imaging

• 11 million MPI procedures annually in 2007
• More than 50% of US nuclear medicine procedures

Supply of Mo-99

- NRU (Chalk River, Canada): 43%
- HFR (Petten, Netherlands): 33%
- SAFARI-1 (Pelindaba, South Africa): 11%
- BR2 (Mol, Belgium): 10%
- OSIRIS (Saclay, France): 3%

Thomas & Maddahi. J Nucl Cardiol 2010 17:993-8
Strategies to Cope with Supply Disruption

• Avoid unnecessary testing
• Use alternative SPECT radiotracers – Thallium-201
• Reduce activity administered
  • Stress only/stress first imaging
  • Advanced reconstructions/cameras
• Alternative testing
  • PET
  • CT
  • Echo
  • MRI
Myocardial Perfusion Imaging with $^{201}$Tl*

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have reverted to $^{201}$Tl – the radiopharmaceutical replaced by $^{99}$Tc\(_{m}\) agents 15–20 years ago. It is produced by cyclotron and so its availability is not affected by reactor shutdowns. The quality of $^{201}$Tl images has improved owing to advances in gamma-camera design and performance, but there is a generation of nuclear medicine consultants who have never worked with $^{201}$Tl. They will require training in the use of this radiopharmaceutical and its image interpretation.
Ottawa Heart Institute: Shortage Worsened Accuracy

True Positives: 59% (Tc-99), 54% (Tl-201), P=0.71
True Negatives: 10% (Tc-99), 5% (Tl-201), P=0.007
False Positives: 16% (Tc-99), 30% (Tl-201), P<0.001
False Negatives: 15% (Tc-99), 4% (Tl-201), P<0.001

Ottawa Heart Institute: Increased Downstream Testing

- Cardiac Cath: 13.3% (P<0.001)
- Coronary CT: 6.0% (P<0.001)
- Stress PET: 1.9% (P=0.001)

What Happened in the US?

- We studied data from Medicare claims 2008-2012
- 20% random sample of beneficiaries ≥65 years
- ~2 million stress tests with SPECT imaging
- Examined rates of downstream invasive coronary angiography within 90 days & alternative testing
- Compared March-August 2010 versus preceding and subsequent periods
Medicare Trends: Use of Tc-99 and Downstream Catheterization

During Shortage:
Odds Ratio of 1.09 [95% CI 1.07-1.10] for Downstream Cath

Excess of 5715 Cardiac Caths in Medicare Alone During 6 Months
Medicare Trends: Alternative Testing

Monthly Rate in Studies Per 1000

SPECT MPI
Coronary CTA
Stress Echocardiography
PET MPI

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Concerning Pattern: Decreasing Rate of Technetium Use

Proportion of SPECT MPI with Tc-99m

Rate of Catheterization within 90 Days After SPECT MPI

Cardiac Catheterization within 90 days

Proportion of SPECT MPI with Tc-99m

Rate of Catheterization within 90 Days After SPECT MPI
Limitations

• Data are observational – causality is uncertain
• Medicare data may not generalize to private payers
• Formal analysis of costs, and projections for future shortages, not performed
  • Given average cost of cath likely to be $100s of millions/year
(c) Medical Production License Sunset

Effective 7 years after January 2, 2013, the Commission may not issue a license for the export of highly enriched uranium from the United States for the purposes of medical isotope production.

(g) Suspension of Medical Production License

At any time after the restriction of export licenses provided for in subsection (c) becomes effective, if there is a critical shortage in the supply of molybdenum-99 available to satisfy the domestic United States medical isotope needs, the restriction of export licenses may be suspended for a period of no more than 12 months, if—

1. the Secretary of Energy certifies to the Congress that the export of United States-origin highly enriched uranium for the purposes of medical isotope production is the only effective temporary means to increase the supply of molybdenum-99 necessary to meet United States medical isotope needs during that period; and

2. the Congress enacts a Joint Resolution approving the temporary suspension of the restriction of export licenses.
Issues Limiting Alternative Testing

- **Stress echocardiography**
  - Difficult to image patients with obesity or COPD
  - Requires skilled technologists

- **CT coronary angiography**
  - Not suitable for higher heart rates, renal disease, prior stents
  - May increase costs due to overestimation bias/lack of flow limitation assessment

- **Stress MRI**
  - Lack of widespread skillset
  - Complexity of managing complications in MR
  - Not suitable for renal disease, pacemakers and other devices

- **Stress PET**
  - High cost of cyclotron for production of N-13 ammonia or O-15 water
  - Limited supply and cost of Sr-82/Rb-82 generators
Possible Solution to the PET Tracer Problem: The Mini-Cyclotron

• 12 MeV, 10μA positive ion cyclotron
• 4.5 Tesla superconducting magnets enable compact form factor
• Standard power
• High temperature superconductor eliminates need for liquid nitrogen/helium
• Highly automated
ION-12\textsuperscript{SC} Validation Timeline at UMHS

- **Feb 1 2016**: Cyclotron Installed
- **Feb 16 2016**: Cyclotron Ramped to Full Field Strength
- **Feb 26 2016**: First Beam on Target
- **Feb 29 2016**: First $^{13}$N-Ammonia Dose
- **Mar 7 2016**: Optimization Begins
- **Mar 23 2016**: 80 mCi Dose of $^{13}$N-Ammonia
- **April 12 2016**: Full Clinical Workflow Simulation
- **Jul 11 2016**: Initial Cyclotron Magnet Tune
- **Aug 1 2016**: Final QA/QC Equipment Validation
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SAVE THE DATE  7-9 May 2017, Vienna AUSTRIA

Call for abstracts & clinical cases
15 Sept – 21 Nov 2016

Early registration fee deadline
27 February 2017