Adenosine stress protocols for myocardial perfusion imaging

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ISSUES

About 1 million patients undergo adenosine stress myocardial perfusion imaging each year. Some publications have used reduced lengths of adenosine infusion at variance with the current American Society of Nuclear Cardiology (ASNC) standards. Some nuclear laboratory directors are using or are considering use of the abbreviated adenosine protocols. Also, the US Food and Drug Administration has approved the use of adenosine with thallium. However, the use of adenosine with technetium 99m sestamibi and tetrofosmin is currently off-label.

BACKGROUND

A review of several large multicenter, prospective, blinded studies comparing adenosine (by a continuous, 6-minute infusion of 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) with exercise thallium 201 single photon emission computed tomography (in a crossover fashion) has confirmed the safety of adenosine imaging and demonstrated a high degree of diagnostic agreement between these two stress modalities. Several other studies have also demonstrated the efficiency and tolerability of the adenosine infusion at 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[1-10]

The time to maximal vasodilation with adenosine is 84 ± 46 seconds (range, 23-125 seconds). The time to recovery from peak dilation once adenosine infusion is stopped is 145 ± 67 seconds (range, 54-310 seconds).[11,12] The higher first-pass extraction and permeability of Tl-201 compared with Tc-99m reflect a different transport mechanism.[13] The first-pass myocardial extraction fraction for Tl-201 is about 85%, and that for Tc-99m sestamibi and tetrofosmin is about 65%. The relationship between blood flow and myocardial uptake is almost linear at a low and moderate blood flow level to at least 3 $mL \cdot min^{-1} \cdot g^{-1}$ for Tl-201 and 2 $mL \cdot min^{-1} \cdot g^{-1}$ for Tc-99m sestamibi and tetrofosmin. Above this level, there appears to be a decrease in the uptake in relation to blood flow.[14,15]

On the basis of the kinetics of adenosine, newer protocols have been proposed for reduction in time, cost, and symptoms by use of a 4-minute protocol with Tl-201 and a 3-minute protocol with Tl-201 or Tc-99m sestamibi. A 4-minute protocol proposed by O'Keefe et al[16] used adenosine at 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and Tl-201 injected at the 3-minute mark of the 4-minute protocol. They noted no significant difference in side effects or diagnostic accuracy between 4-minute and 6-minute protocols. However, this unblinded study was retrospective and limited because cohorts were not concurrent. There was also post-test referral bias. Many laboratories have used the shorter protocol for more than 10 years with satisfactory but unpublished results. Thus reasonable precedence has been set for the use of the 4-minute protocol at this time as suggested in the ASNC imaging guidelines.[17]

A 3-minute protocol proposed by Treuth et al[18] used adenosine infusion at 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and prospectively randomized patients to 3-minute or 6-minute infusion. In this protocol Tl-201 or Tc-99m was injected at the 1.5-minute mark. The study power for each tracer was too low. Perfusion defect size was smaller with the 3-minute protocol, although there was no change in sensitivity. The 3-minute protocol was better tolerated

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than the 6-minute protocol. Both 3-minute and 6-minute protocols had a problem with post-test referral bias and low specificity.

SUMMARY

Although there are no large randomized, blinded, prospective trials comparing 3- or 4-minute protocols with the 6-minute adenosine infusion protocol, there has been a history of clinical use of a 4-minute protocol with favorable results.

Kinetic data for adenosine define that the minimum time to injection of tracer should be 2 minutes to provide adequate time to achieve maximal vasodilation, and that the maximal vasodilation should continue for 2 minutes to ensure adequate uptake for both Tc-99m– and Tl-201–labeled radiotracers.

RECOMMENDATIONS

ASNC continues to recommend the 6-minute infusion protocol for adenosine stress myocardial perfusion imaging as defined in the imaging guidelines.[17]

The 4-minute adenosine protocol is a reasonable alternative based on the known kinetics of adenosine, the established blood clearance of radiotracers, and the presently published patient series that show comparable sensitivities. In this protocol we recommend injection of tracer at the 2-minute mark, allowing 2 minutes for circulation time. Variations of this protocol extending beyond 4 minutes are acceptable, provided that adenosine infusion is administered for at least 2 minutes after tracer injection.

We do not recommend a 3-minute adenosine infusion protocol. Kinetic data suggest that this shorter protocol does not provide adequate time for infusion and tracer administration to achieve a good-quality and reproducible vasodilator response.

We encourage further research studies to be conducted in large multicenter trials to investigate alternative adenosine infusion protocols. Prospective, blinded studies with adequate power are necessary to compare newer adenosine infusion lengths at 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ compared with 6-minute infusion in a crossover fashion to demonstrate the efficacy and tolerability of these protocols.

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