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Clinical

Pooled comparison of regadenoson versus adenosine for measuring fractional flow reserve and coronary flow in the catheterization laboratory

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ABSTRACT

Background: Adenosine is the gold standard for augmenting coronary flow during fractional flow reserve (FFR) testing of intermediate coronary stenoses. However, intravenous infusion is time-consuming and intracoronary injection is subject to variability. Regadenoson is a newer adenosine alternative administered as a single intravenous bolus during nuclear stress testing, but its efficacy and safety during FFR testing have been evaluated only in small, single-center studies.

Methods: We pooled data from 5 academic hospitals, in which patients undergoing clinically-indicated FFR prospectively underwent comparison of intravenous adenosine infusion (140–175 mcg/kg/min) versus regadenoson bolus (400 mcg). Hemodynamics and symptoms with adenosine were recorded until maximal hyperemia occurred, and after returning to baseline hemodynamics, regadenoson was administered and monitoring was repeated. In a subset of patients with coronary flow data, average peak velocity (APV) at the distal flow sensor was recorded.

Results: Of 149 patients enrolled, mean age was 59 ± 9 years, 76% were male, and 54% underwent testing of the left anterior descending artery. Mean adenosine-FFR and regadenoson-FFR were identical (0.82 ± 0.10) with excellent correlation of individual values ($r = 0.96$, $p < 0.001$) and no difference in patient-reported symptoms. Four patients (2.6%) had discrepancies between the 2 drugs for the clinical decision-making cutoff of FFR ≤ 0.80. Coronary flow responses to adenosine and regadenoson were similar (APV at maximal hyperemia 36 cm/s for both, $p = 0.81$).

Conclusions: Regadenoson single-bolus administration has comparable FFR, symptoms, and coronary flow augmentation when compared with standard intravenous adenosine infusion. With its greater ease of administration, regadenoson may be a more "user-friendly" option for invasive ischemic testing.

1. Introduction

Myocardial ischemia identifies patients at higher risk of experiencing adverse cardiovascular events [1,2], and revascularization of ischemic myocardium is associated with improved clinical outcomes and resource utilization [3–10]. Fractional flow reserve (FFR) measurement at cardiac catheterization allows for direct ischemic testing of coronary stenoses, as a pressure sensor is placed distal to the lesion in the diseased artery and compared with aortic pressure at maximal hyperemia, when coronary flow is at its peak [11,12]. Based on findings from large-scale clinical trials, FFR has been adopted for assessing the physiologic significance of moderate-to-severe coronary stenoses, with intravenous (IV) adenosine infusion accepted as the "gold standard" for achieving maximal hyperemia during invasive ischemic testing [3–5].

Abbreviations: ACE, angiotensin converting enzyme; APV, average peak velocity; CABG, coronary artery bypass grafting; CFR, coronary flow reserve; CHF, congestive heart failure; FFR, fractional flow reserve; HR, heart rate; IC, intracoronary; IV, intravenous; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PCI, percutaneous coronary intervention.

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Despite the proven benefit of FFR-guided management of intermediate stenoses, this technology is used in <25% of percutaneous coronary interventions for stable coronary disease. Resistance to routine FFR testing was historically related to reduced ability to torque or steer the FFR wire, whereas more contemporary concerns are focused on the inconvenience of establishing central venous access, and the added time delay related to mixing and administering a weight-based IV infusion of adenosine. Direct intracoronary (IC) injection of adenosine has been adopted by some operators, but this approach is subject to variability or inadequate achievement of hyperemia in some patients [13–15].

Regadenoson, a novel agonist of the A_{2a} receptor of adenosine, recently has been introduced as an adenosine alternative during noninvasive nuclear myocardial imaging. Given its ease of use with a single-dose bolus administered through peripheral IV access, regadenoson has gained wide acceptance over adenosine as the pharmacologic agent of choice for many nuclear stress test laboratories. However, few studies have evaluated the use of regadenoson for FFR testing in the catheterization laboratory, and most of these analyses involved relatively small numbers of patients at individual hospitals [16–19]. The largest and most recent study provided a more comprehensive evaluation of repeat vasodilator testing, duration of hemodynamic effects, plus evaluations of central versus peripheral venous injections [19]. Nonetheless, a multicenter comparison of regadenoson and adenosine has not been described, and to our knowledge, no studies have compared the effects of both drugs on directly-measured coronary flow during clinically-indicated FFR testing.

To address these gaps in knowledge, we conducted a prospective comparison of adenosine and regadenoson among patients referred for FFR-guided coronary revascularization at 2 academic hospitals. We then pooled these findings with the existing single-center studies of regadenoson during FFR, and among the subset of patients with coronary flow measurements performed, we also evaluated the effects of these 2 drugs on coronary flow.

2. Methods

2.1. Patient selection

At 2 academic hospitals (Saint Louis University and the University of Florida Health- Jacksonville), unselected adult patients undergoing coronary angiography were enrolled in a prospective, open-label evaluation of adenosine and regadenoson during clinically-indicated FFR testing between July 2011 and April 2013. Separately, using MedLine search engines and references from other FFR studies, we identified 3 published single-center studies that prospectively compared adenosine and regadenoson for calculating FFR [16–18]. Individual patient-level data were collected from the published articles and by contacting the study investigators for a collaborative multicenter comparison of these 2 drugs during FFR testing (Fig. 1).

In all 5 hospitals, the overall protocol for inducing hyperemia and patient monitoring was similar. Each patient received both medications sequentially—first with weight-based IV adenosine and followed by a single IV regadenoson bolus (as described below)—which allowed each individual to serve as his/her own control by undergoing FFR measurement first with adenosine and then with regadenoson. The study protocol was approved by each university's institutional review board. Informed consent was obtained from all patients prior to angiography, and only those individuals with clinical indications for ad hoc FFR testing ultimately were enrolled in the study. Patients with acute myocardial infarction, systemic hypotension, significant second- or third-degree atrioventricular block (without a permanent pacemaker), pregnancy, extreme target vessel tortuosity, prior heart transplantation, active wheezing or bronchospasm, or medications known to confound the induction of maximal hyperemia (theophylline, aminophylline, pentoxiphylline, dipyridamole, caffeinated beverages within 12 hours) were not eligible for the study due to concerns about medical safety and/or diagnostic accuracy of FFR testing. Minor differences between the study protocols at the various hospital sites were noted in terms of angiographic stenosis severity required for inclusion (40–70% vs. 50–70% vs. 50–80%), frequency of data collection during monitoring (every 20, 30, or 60 seconds), and the washout period between adenosine and regadenoson (ranging from 5 to 10 minutes). One hospital used a slightly higher dose of adenosine during the intravenous infusion (described below).

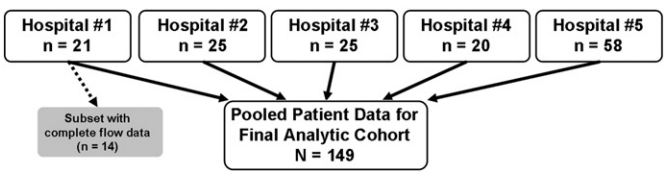

Fig. 1. Inclusion of hospital sites in the pooled analysis. Patient-level demographic and fractional flow reserve data were available from all 5 hospitals, and 1 hospital collected simultaneous coronary flow data in a subset of patients.

2.2. Procedural details

Among patients with an intermediate stenosis at diagnostic coronary angiography for whom clinically-indicated FFR testing was planned, antithrombotic medications were administered according to standard catheterization laboratory practice. Continuous hemodynamic monitoring and clinical assessments also were performed according to standard FFR protocol. Coronary pressure was measured distal to the stenosis of interest using a clinically-approved, 0.014-inch high-fidelity pressure wire (either PrimeWire from Volcano Corp., Rancho Cordova, California; or PressureWire from Radi Medical Systems, Uppsala, Sweden—later known as Aeris PressureWire from St. Jude Medical, St. Paul, Minnesota). In a subset of patients at one hospital, both coronary pressure and flow were obtained using a wire with both pressure and flow transducers embedded in the same 0.014-inch wire (ComboWire from Volcano Corp., Rancho Cordova, California).

After equalizing the pressure wire at the distal tip of the guide catheter in the ascending aorta [20], the coronary ostium was engaged and the wire was advanced beyond the stenosis of interest. Intracoronary nitroglycerin was injected per standard protocol. The guide catheter was then slightly disengaged from the coronary ostium and fidelity of pressure and flow tracings were verified (i.e., to ensure lack of pressure damping). Aortic pressure was measured proximally using the interventional guide catheter and distally using the intracoronary wire. Mean pressures were collected continuously from the distal (coronary) and proximal (aortic) locations, and FFR was calculated as the ratio of distal to proximal mean arterial pressure at peak hyperemia. In the subset of patients with coronary flow data collected, average peak velocity (APV) also was measured continuously, both before and during the induction of hyperemia, and coronary flow reserve (CFR) was calculated as the ratio of peak-to-baseline APV.

2.3. Pharmacologic infusions and monitoring

All patients underwent standard adenosine 140 mcg/kg/min infusion (Adenoscan; Astellas Pharmaceuticals, Deerfield, Illinois) through peripheral IV access, except for one hospital where 175 mcg/kg/min was used. Hemodynamics, symptoms, adverse effects (e.g., wheezing, heart block), and pressure and/or flow measurements were collected every 20–60 seconds (depending on the protocol at each enrolling hospital) for a minimum of 2 minutes and for up to 5 minutes, or until maximal hyperemia occurred. These data also were collected after completion of the infusion, during the washout period for the adenosine infusion. After returning to within 15% of baseline hemodynamics, a single IV bolus of regadenoson 400 mcg was administered over 10 seconds followed by a 5 mL saline flush, as recommended by the package insert