JACC: CARDIOVASCULAR INTERVENTIONS

VOL. 8, NO. 4, 2015

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcin.2014.10.027

Fractional Flow Reserve in the Transradial Era: Will Hand Vein Adenosine Infusion Suffice?

A Comparative Study of the Extent, Rapidity, and Stability of Hyperemia From Hand and Femoral Venous Routes of Adenosine Administration

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ABSTRACT

OBJECTIVES The aim of this study was to assess adenosine infusion via a cannula in the back of the hand compared with central venous access to achieve peak hyperemia during fractional flow reserve (FFR).

BACKGROUND Adenosine is often used to induce maximal hyperemia when measuring FFR. The gold standard is continuous infusion via a large central vein; however, the increasing use of the transradial route for angiography makes it desirable to have an alternative route for adenosine. Peripheral venous access is frequently obtained in the hand, but concern exists as to whether adenosine delivery from this site can achieve adequate vasodilation for accurate FFR measurement. Our aim was to address this.

METHODS Subjects were selected from patients presenting for coronary angiography/intervention who required a pressure-wire study. Subjects received intravenous adenosine infusion sequentially via 2 routes: first, via a 20-gauge hand cannula, and then, after a washout period, via a 5- or 6-F femoral venous sheath. Adenosine was administered at 140 μg/kg/min from each site. Data interpretation was blinded. Minimal FFR achieved with intravenous adenosine from each infusion site was recorded as was the time to peak hyperemia.

RESULTS Paired (hand and femoral adenosine) recordings taken from 84 vessels in 61 patients were suitable for blinded analysis. The mean FFR measured using adenosine administered via hand and femoral routes was 0.85 with an SD of 0.08 (intraclass correlation = 0.986). Time to peak hyperemia was longer on average with hand-administered adenosine compared with femoral adenosine administration (63 s vs. 43 s; mean difference, 22 s with a 95% confidence interval: 18 s to 27 s; $p < 0.0001$). Formal comparison of FFR stability using Mann-Whitney analysis (2 tailed) gives $p = 0.43$, indicating no significant evidence of a difference in stability between the 2 routes.

CONCLUSIONS Hand vein adenosine infusion produced FFR values very similar to those obtained using central femoral vein adenosine administration, with no systematic bias toward higher or lower reading from 1 site. This has important practical implications for radial access cases involving pressure-wire studies. (J Am Coll Cardiol Intv 2015;8:527–35)

Fractional flow reserve (FFR) has become an increasingly popular tool to guide percutaneous coronary intervention (PCI). A large evidence base has now been amassed for the utility of this index to help decide which lesions can be safely left without stenting (1–3) and to guide the use of PCI in multivessel disease (4). To accurately determine FFR, it is essential to induce maximal

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Manuscript received May 20, 2014; revised manuscript received September 26, 2014, accepted October 23, 2014.

ABBREVIATIONS AND ACRONYMS

FFR = fractional flow reserve

Pa = pressure aorta

PCI = percutaneous coronary intervention

Pd = pressure distal

hyperemia in the vascular bed under investigation (5). This is most commonly achieved with adenosine, either given as an intravenous infusion or as an intracoronary bolus. In many cases, an intravenous infusion of adenosine is preferred to bolus administration.

Transradial access for PCI is also rapidly growing in popularity worldwide and has become the predominant mode of access in many countries. Accumulating evidence suggests a clinical benefit, particularly in higher risk settings such as acute coronary syndrome and ST-segment elevation myocardial infarction (6–8). In cases in which radial access is used, the femoral area is not routinely prepared with intravenous access via a peripheral vein in the arm. In cases in which pressure-wire studies are required, concerns exist over use of forearm (especially hand vein) administration, given the short half-life of adenosine in relation to the venous access site-to-heart transit time. De Bruyne et al. (9) found that intravenous administration of adenosine at 140 μg/kg/min was equally as effective as higher doses in producing maximal hyperemia, and antecubital venous access appeared to be as good as femoral in this respect (forearm and hand vein access was not studied). However, they do mention 3 cases in which antecubital vein use led to "wide fluctuations of coronary resistance," which were not seen with a femoral approach. Femoral vein use was therefore recommended where a pullback is required (due to more stable steady-state conditions).

The purpose of this study was to compare central versus peripheral adenosine infusion, both in the assessment of peak FFR and stability of peak FFR recording once achieved. To model frequent clinical practice, we chose to compare the use of a small pink (20-gauge) cannula in the back of the hand versus a 5- or 6-French sheath in the femoral vein.

METHODS

This study was carried out at a single regional cardiac center in the United Kingdom. Patients who were to undergo elective pressure-wire study or for possible ad hoc pressure-wire study during diagnostic angiography were considered for inclusion in the study. Ethics approval was granted from the institutional ethics review process, and informed patient consent was obtained.

CLINICAL PROTOCOL. Patients had intravenous access established before the pressure-wire procedure using a pink (20-gauge) cannula placed in the hand or, in the occasional case in which no suitable hand vein was found, at wrist level (but no more proximally in the arm than this). Coronary angiography was performed as per usual clinical protocol. The radial or femoral route of arterial access was chosen based on individual operator preference. For femoral venous administration of adenosine, a venous sheath (5- or 6- F) with a side arm was used. The Radi PressureWire system (St. Jude Medical, St. Paul, Minnesota) was used in all cases.

Based on usual clinical criteria (10), coronary lesions thought to require further evaluation by a pressure-wire procedure were studied as follows. 1) A pressure wire was passed in the usual manner, with equalization in the proximal portion of the vessel followed by passage distal to the lesion of interest. 2) Adenosine was first administered via the hand cannula at a rate of 140 μg/kg/min for 2 min. Tracings were recorded from the time of commencement of adenosine infusion. 3) After 2 min of adenosine infusion in the hand, the adenosine was stopped. At least 1 min was allowed to pass, allowing resting pressure distal/pressure aorta (Pd/Pa) distal to the lesion to return to baseline (pre-adenosine) levels. The wire position was not altered during this time (i.e., no pullback was performed at this stage). 4) Adenosine was then administered via the femoral venous sheath at a rate of 140 μg/kg/min. A new tracing was recorded from the time of commencement of this adenosine infusion for 2 min. 5) At the end of this time, pullback to the guide catheter was performed to exclude significant drift (and localize the area of step-up if required).

ANALYSIS PROTOCOL. Intracoronary pressure recordings were downloaded from the relevant catheter laboratory hardware (Radi Analyzer, St. Jude Medical) and viewed on RadiView software. Review of all tracings was performed by a highly experienced cardiac physiologist who was blinded to route of administration of adenosine and to all procedural details.

For each tracing, the full 2-min recording was examined, and the period of lowest stable Pd/Pa readings was taken to reflect maximal hyperemia. Ten consecutive beats were averaged during this period to derive FFR (5 beats on either side of the point of lowest Pd/Pa) to counteract fluctuation in FFR measurement and ensure that a smooth recording was obtained. The time to peak hyperemia was taken as the time to the lowest stable Pd/Pa value.

ASSESSMENT OF STABILITY OF PEAK FFR. To assess stability of hyperemia, the next 30 s of tracing subsequent to the period of maximal hyperemia was

evaluated. A 30-s period was chosen as it was thought that clinical pullback measurements would usually be completed within this time and the relevant period of recording in which to assess stability and its potential impact on lesion assessment. The highest value of Pd/Pa over this 30-s period was identified, and a 3-beat average around this point was calculated. The use of a 3-beat average ensured that the degree of Pd/Pa fluctuation was faithfully captured rather than being "smoothed out" by averaging over a larger number of beats. A stability index was calculated simply as (highest 3-beat average of Pd/Pa during 30 s after maximal hyperemia) − (FFR, that is, the 10-beat average of Pd/Pa at peak hyperemia).

STATISTICAL ANALYSIS. Statistical analysis was performed using GraphPad Prism (Graphpad Software Inc., La Jolla, California). Bland-Altman analysis was used to compare the 2 routes of adenosine administration in terms of steady-state FFR obtained (11).

For time to peak hyperemia and stability index, paired nonparametric testing was performed (based on the findings of non-Gaussian distributions for these parameters).

RESULTS

PATIENT AND DEMOGRAPHIC CHARACTERISTICS. Paired (hand and femoral adenosine) recordings taken from 84 vessels in 61 patients were suitable for blinded analysis. The mean age was 64.5 ± 10 years (range 39 to 86 years), and sex ratio was 46 (75%) male to 15 (25%) female. Additional baseline and procedural data are summarized in Table 1.

Figure 1 illustrates a typical example of a tracing reviewed on the RadiView software system. The region of steady-state maximal hyperemia is shown, as is the area of highest Pd/Pa over the subsequent 30 s.

EXTENT OF HYPEREMIA. The mean FFR measured using the hand and femoral routes of adenosine administration was 0.85 with an SD of 0.08.

Figure 2 is a before-and-after plot for each FFR hand recording and subsequent comparable FFR femoral recording, revealing very similar FFR output for the majority of cases. Figure 3A illustrates corresponding steady-state FFR measurements for each lesion as (x,y) coordinates. The line of identity is shown as a solid line on this graph. The majority of readings lie close to this line, indicating a good agreement between FFR values derived from the 2 routes of adenosine administration (intraclass correlation = 0.986; $p < 0.001$). Figure 3B shows a Bland-Altman plot of the same data and allows easier visualization of the direction of disagreement between FFR from the 2 routes. Many cases exist in which the steady-state FFR is actually lower using hand vein adenosine infusion than when using the femoral venous sheath (represented as data points below the x-axis on the graph). There are similarly many other cases in which the converse is true (i.e., FFR from femoral adenosine administration is lower). Formal evaluation of the agreement between these 2 measures of FFR by Bland-Altman analysis indicated an estimated bias of 0.002 with 95% limits of agreement extending from −0.03 to +0.04, with no evidence for a systematic direction of bias of FFR measurements from the 2 different routes.

In patients undergoing assessment of more than 1 coronary stenosis, the route of adenosine administration producing the lowest value of steady-state FFR could vary among lesions. Figure 4 shows an expanded portion of Figure 3A centered on the clinical threshold FFR value of 0.80. Given the similar FFR values produced by the 2 routes of adenosine administration and the lack of systematic bias between these, it is an inevitable consequence that the use of a strict cutoff value (such as the widely used FFR ≤0.80)

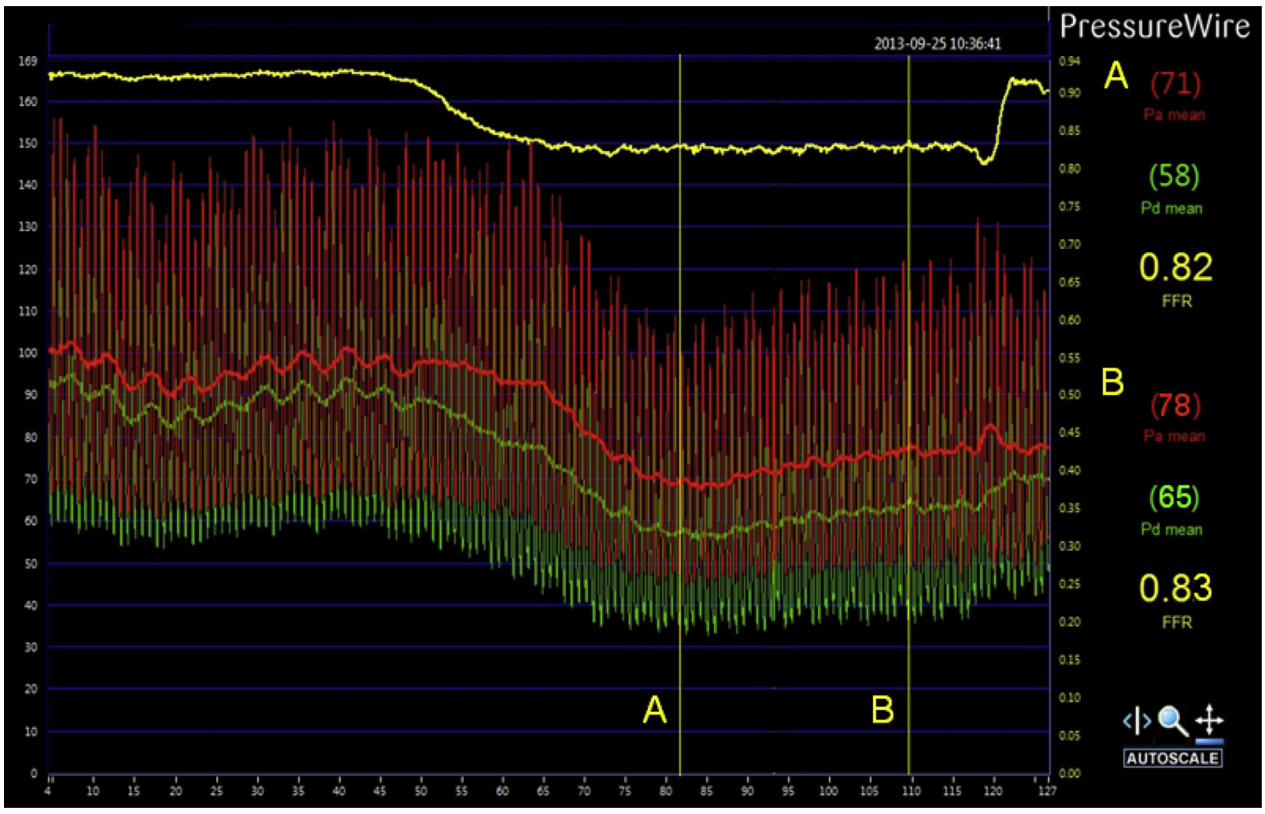
TABLE 1 Baseline Data of Study Patients

No. of patients	61
No. of vessels	84
Mean age, yrs	64.5
Mean weight, kg	83
Mean height, cm	172
Male	46 (75)
Clinical setting	
Stable angina	52 (85)
Acute coronary syndrome	9 (15)
Vessels attempted	
LAD/diagonal	45 (54)
LCx/marginal	19 (23)
RCA/PDA	16 (19)
Ramus	2 (2)
LMS	1 (1)
LIMA graft	1 (1)
FFR	
Hand, SD	0.85 ± 0.076
Femoral, SD	0.85 ± 0.078
Femoral FFR - hand FFR	−0.08 to 0.04
Femoral FFR - hand FFR	0 (−0.01 to 0.01)
Mean time to peak hyperemia, s	
Hand	67
Femoral	44
Stability Index	
Hand	0.016
Femoral	0.014

Values are n, n (%), mean ± SD, range, or mean (interquartile range).

FFR = fractional flow reserve; LAD = left anterior descending artery; LCx = left circumflex artery; LIMA = left internal mammary artery; LMS = left main stem artery; PDA = posterior descending artery; RCA = right coronary artery.

FIGURE 1 Fractional Flow Reserve Recording in a Sample Patient

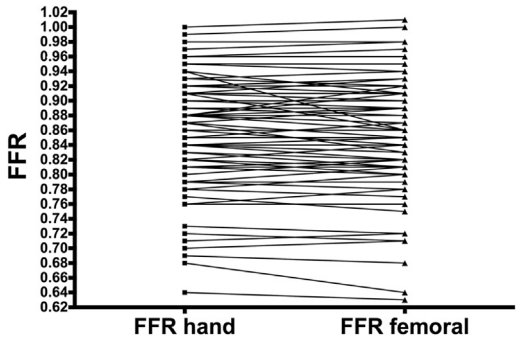


A typical example of a tracing reviewed on the RadiView software system (St. Jude Medical, St. Paul, Minnesota). The region of steady-state maximal hyperemia **(first yellow bar labeled A)** is shown, as is the area of highest pressure distal (Pd)/pressure aortic (Pa) over the subsequent 30 s **(subsequent yellow bar labeled B)**. The stability index in this case is +0.01. FFR = fractional flow reserve.

for decision making will lead to cases when a different decision would be made depending on whether adenosine was administered via hand vein or femoral vein routes. This is illustrated graphically in Figure 4, which shows 5 cases (enclosed by a square on the graph) in our study in which FFR was positive with hand vein adenosine infusion but negative with femorally administered adenosine. Conversely, 4 cases in which the FFR was negative with hand vein adenosine infusion but positive with femorally administered adenosine (enclosed by oval on the graph) are also highlighted. No cases had a significant crossover difference in FFR from 1 side of the gray zone (0.76 to 0.80) to the other (i.e., no value dropped from an FFR of >0.8 with hand adenosine to <0.76 with a femoral adenosine). Similarly, no value rose from a FFR of <0.76 with hand vein adenosine infusion to more than 0.8 with femorally administered adenosine (Figure 2). The clinical implications of this finding are considered further in the Discussion section.

RAPIDITY OF HYPEREMIA. Time to peak hyperemia was longer with hand compared with femoral adenosine (67 s vs. 44 s; $p < 0.001$). In Figure 5, data points lie mainly on the right-hand side of the line of identity, indicating that the time to peak hyperemia was shorter with the femoral route of adenosine administration than with the hand vein adenosine infusion, whereas in rare cases, the converse was true. In patients in whom more than 1 lesion was assessed, it was found that 1 particular route of adenosine administration was consistently more rapid in achieving steady state than the other, and the times to peak hyperemia from any particular route were remarkably consistent in an individual patient. In 1 patient, the development of hyperemia with hand vein adenosine infusion was delayed such that there was no change from resting Pd/Pa value (distal to the lesion) until almost 2 min of adenosine infusion had elapsed. The recording was continued beyond 2 min in this case, and peak hyperemia was

FIGURE 2 Before and After Plot Comparing FFR Hand and Subsequent FFR Femoral Infusion for Each Recording



No cases of FFR >0.85 with hand adenosine infusion were <0.80 using the femoral route of infusion or vice versa. Also, no cases had a significant crossover difference in FFR from 1 side of the gray zone (0.76 to 0.80) to the other (i.e., no value dropped from a FFR of >0.8 with hand adenosine infusion to <0.76 with femoral adenosine infusion). Similarly, no value rose from an FFR of <0.76 with hand adenosine infusion to >0.8 with femoral adenosine infusion. FFR = fractional flow reserve.

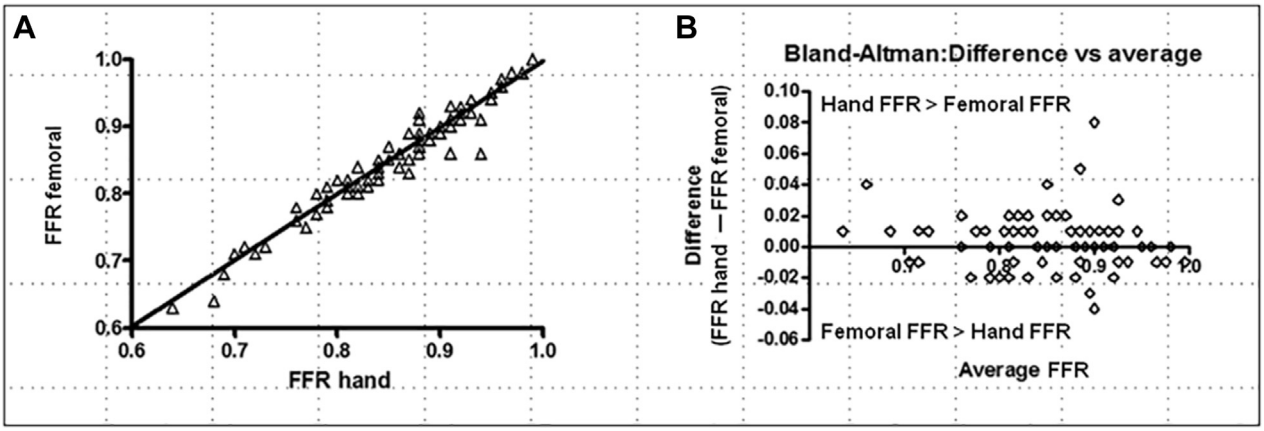
noted at 147 s in this case compared with 54 s from the groin. When a second lesion was assessed in this patient, times to hyperemia from the hand and groin were 140 s and 53 s, respectively (highlighting the consistency in time to hyperemia for each route and eliminating any concern that the first delayed hyperemic result from the hand was artifact due to "dead space" in the adenosine infusion line).

STABILITY OF HYPEREMIA. The stability of Pd/Pa readings with ongoing adenosine infusion via hand versus femoral routes is indicated in Figure 6. Paired pullback recordings were available in 75 cases. The solid line in Figure 6A represents the line of identity, and the scatter of data points on either side of this line demonstrates that the stability of readings may be greater with either route on an individual basis. Data points on the line of identity represent cases in which stability was equivalent from either approach. Figure 6B shows the summarized data for stability for all cases. Formal comparison using Mann-Whitney analysis (2-tailed) gives a p value of 0.43, indicating no significant evidence of a difference in stability between the 2 routes.

DISCUSSION

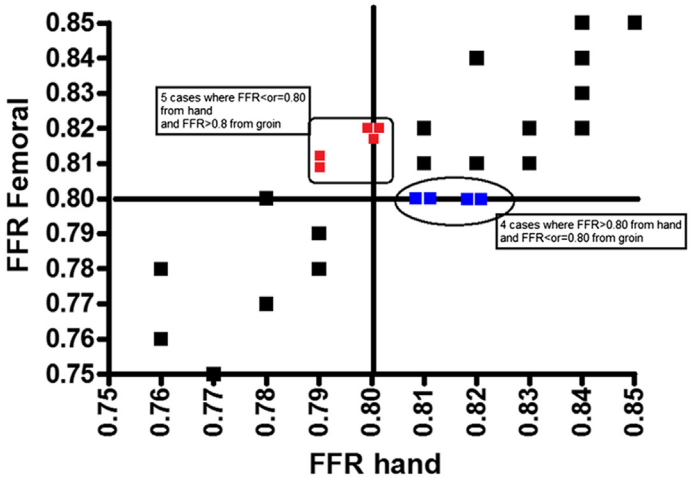
Transradial access has become standard practice in many European countries and is rapidly gaining popularity in the United States. Use of the pressure-wire test for FFR-guided decision making has an established evidence base from large contemporary randomized trials, and its use is increasing worldwide. The use of a combination of transradial access and FFR-based lesion assessment is rapidly becoming a standard of care in many clinical situations, and the issue of adenosine delivery is therefore relevant and topical. Complete avoidance of femoral site access in a transradial case is highly desirable and has led to frequent use of peripheral venous adenosine administration for FFR, despite lingering doubts as

FIGURE 3 Comparison of Hand and Femoral Adenosine Infusions on FFR Recordings



(A) Corresponding steady-state FFR measurements for each lesion as (x,y) coordinates (i.e., hand infusion route of adenosine (x-axis) versus the femoral route (y-axis). The line of identity (for an exact match between the 2 readings) is shown as a **solid line** on this graph. **(B)** A Bland-Altman plot of the same data allows easier visualization of the direction of disagreement between FFR from the 2 routes. FFR = fractional flow reserve.

FIGURE 4 Different FFR Results From Different Access Points



Five cases (represented by a **red squares** on the graph) in our study in which FFR was positive with hand adenosine infusion but negative with femoral adenosine infusion. Conversely, 4 cases in which the FFR was negative with hand adenosine infusion but positive with femoral adenosine infusion (represented by **blue squares** on the graph) are also highlighted. FFR = fractional flow reserve.

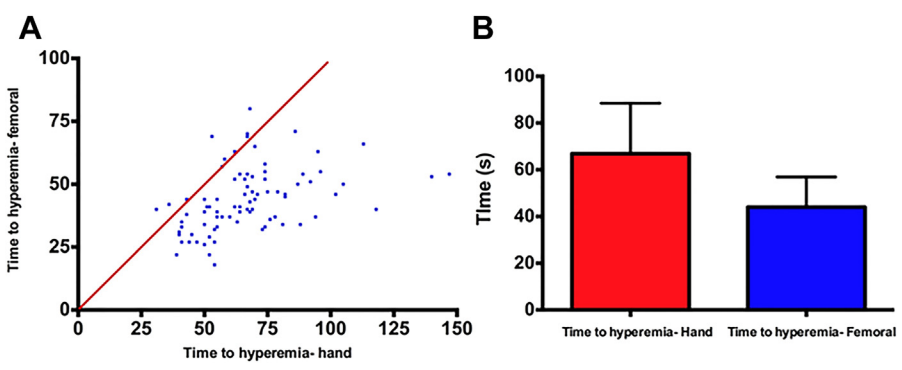
to whether a small cannula would actually generate adequate and sufficiently stable coronary hyperemia compared with a central venous infusion.

In this study, close but not identical agreement was found between FFR values obtained using adenosine administered via the hand and femoral routes, and no systematic direction of bias was evident from Bland-Altman analysis. These 2 findings taken together lead to the inevitability of cases in which the 2 routes will produce slightly different FFR values that happen to lie on opposite sides of the usual decision threshold of FFR ≤0.80. It has been well documented that intrinsic variability of FFR recordings does exist when repeated on the same lesion, with the DEFER study showing only 80% certainty (probability that the FFR-guided revascularization strategy will not change if the test is repeated 10 min later) at an FFR range of 0.77 to 0.83 (12). The occasional FFR difference between access routes may actually be due to the intrinsic variability of the test itself and independent of whether adenosine is administered via the back of the hand or groin. This could also explain the other interesting finding in our study, where the access route of adenosine infusion producing the lowest value of steady-state FFR could vary between lesions in the same patient undergoing assessment of more than 1 coronary stenosis.

Our findings support a strategy of using peripheral venous adenosine administration as the default approach (including use of the veins in the hand, if more proximal access in the forearm or antecubital fossa is difficult). The close agreement of FFR using hand and femoral routes (with 95% confidence intervals extending to differences of −0.03 to +0.04) indicate that if FFR using peripheral route adenosine administration is ≥0.85, then the value obtained using central (femoral) route for adenosine administration in this case is unlikely to be ≤0.80. Indeed, no such cases were demonstrated in our study, as seen in Figure 2.

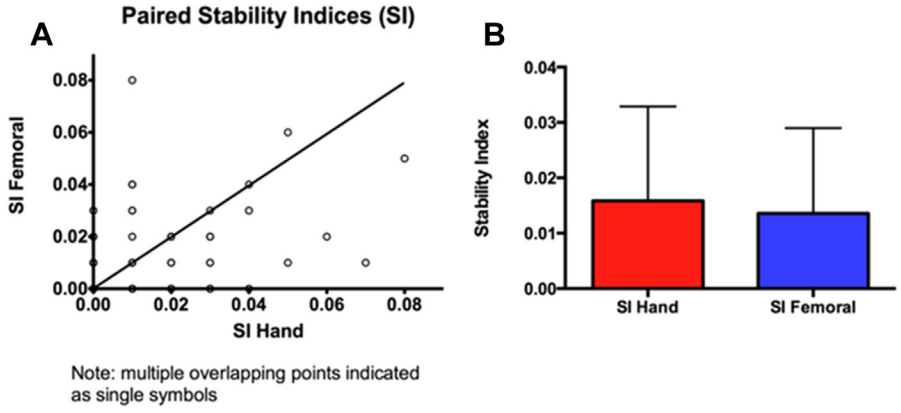
In cases involving the so-called gray zone (0.76 to 0.80), prudent clinical judgment is advised. Previous suggestions for dealing with borderline FFR results such as this include the administration of higher doses of adenosine by infusion or an added

FIGURE 5 Time to Peak Hyperemia



(A) The 2 routes of adenosine infusion are shown for individual cases as (x,y) coordinates. The **straight red line** indicates the line of identity. **(B)** The mean times to peak hyperemia with hand and femoral adenosine infusion. FFR = fractional flow reserve.

FIGURE 6 **Paired Stability Indexes**



Stability index (highest 3-beat average of pressure distal/pressure aortic [Pd/Pa] during 30 s after maximal hyperemia) minus (FFR) with hand versus femoral infusion routes **(A)**. The **solid line** represents the line of identity. **(B)** The mean SI data for stability for all cases; the mean SI for hand infusion is 0.016 and 0.014 for groin infusion. FFR = fractional flow reserve; CI = stability index.

intracoronary bolus (in an effort to ensure maximal hyperemia has been achieved). The former approach has been shown in a single study to produce significantly lower FFR recordings when comparing an adenosine infusion rate of 140 μg/kg/min with a rate of 170 μg/kg/min via the antecubital fossa (13). This study was limited by minimal (0.0064, 95% confidence interval: 0.0004 to 0.0124, p = 0.038) absolute FFR differences between the 2 infusion rates, and steady-state FFR recordings of more than 10 beats were not performed. Indeed, increasing adenosine rates to more than 140 μg/kg/min failed to produce incremental hyperemia when formally studied in 2 further randomized, controlled trials (9,14). As such, the routine practice at our center is to infuse at 140 μg/kg/min from both central and peripheral access routes. The latter approach (intracoronary bolus while the intravenous adenosine infusion still running) was assessed in a subgroup of patients in a recent Korean study where it failed to improve hyperemic efficiency but was nevertheless associated with an increased risk of prolonged atrioventricular block (15).

An alternate suggestion when faced with a borderline FFR recording has been to switch to central venous access, if a peripheral adenosine infusion has initially been used. This approach is often based on subjective conjecture, not evidence based and certainly not supported by the results of this study. Indeed, 5 cases of peripherally infused adenosine produced FFR results <0.80 compared with central administration results of >0.80 (**Figure 4**).

Time to hyperemia was longer on average with hand compared with femoral adenosine administration. This additional time required for hyperemia with hand route of adenosine administration will not produce significant intraprocedural delay, particularly when contrasted with time to establish femoral venous access. One caveat with hand route of adenosine administration relates to occasional cases in which there is a long delay before any change in resting Pd/Pa after adenosine infusion commencement (encountered in 1 of our study cases, as described earlier). In this situation, adenosine infusion must be continued for a longer duration to allow the development of hyperemia. Once steady state is achieved in this manner, the degree of hyperemia appears comparable to that with the femoral route.

Finally, the findings regarding stability of hyperemia with hand and femoral adenosine infusion are reassuring. Although not standard practice, we used a 10-beat average for obtaining FFR to ensure that any potential fluctuation in recordings were negated as much as possible and allow adequate assessment of the stability index. The results indicate that hand adenosine infusion should provide comparable stability, and femoral venous access need not be considered a requirement in situations in which a pullback tracing is desired. The degree of variability in the FFR readings was noted to be markedly different between individuals, with some having virtually no variability once at steady state, and others having a notably cyclical change in Pd/Pa over

time (the so-called accordion effect). In this latter group, this phenomenon was noted with both hand and femoral adenosine infusion (to variable relative extents in individual patients, as indicated in Figure 6). This is often considered a potential shortcoming restricted only to the peripheral venous approach (9); however, in line with previous small studies, our results have disputed this (16).

STUDY LIMITATIONS. This study is not able to comment on the potential utility of higher doses of adenosine infusion or systematic use of an intracoronary bolus (added to intravenous infusions) in the assessment of FFR. Also, the FFR procedures were performed by several operators at a single center, and interobserver variability was not assessed. However, individual operator technique was formalized using local and study guidelines, and data analysis was performed by a blinded clinical physiologist. We did not compare infusion of adenosine from differing peripheral access sites (e.g., back of the hand, wrist, forearm, antecubital fossa) or determine whether body habitus played an important role, and this may be an opportunity for future research.

CONCLUSIONS

This study provides reassurance about the use of hand vein adenosine infusion to generate maximal coronary hyperemia, including situations in which information from a pullback is required. When FFR recordings in and around the gray zone (0.76 to 0.80) are obtained, converting to femoral access for adenosine infusion is not supported, and any divergence seen on the FFR result by switching access site could simply be explained by the variability of the index procedure itself. Additional hyperemic stimulus with intracoronary adenosine is a more appropriate option in addition to sound clinical judgment, with the decision to revascularize based on the evaluation of each individual patient and his or her symptoms.

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PERSPECTIVES

WHAT'S KNOWN? Fractional flow reserve (FFR) is a well-established tool for physiological assessment of the severity of a coronary artery stenosis. Maximal hyperemia is required for optimal FFR-guided lesion assessment, usually via administration of adenosine. Debate remains as to whether optimal adenosine infusion to achieve stable, maximal hyperemia should be via a central venous line, or will peripheral administration via a small cannula will suffice?

WHAT'S NEW? This study provides reassurance about the use of hand vein adenosine infusion to generate maximal coronary hyperemia for the assessment of FFR. Converting to femoral access for adenosine infusion is not supported by this study, and any divergence seen on the FFR result by switching access site could simply be explained by the variability of the index procedure itself.

WHAT'S NEXT? This study is not able to comment on the potential utility of higher doses of adenosine infusion or systematic use of an intracoronary bolus (added to intravenous infusions) in the assessment of FFR. Future research could assess infusion of adenosine from differing peripheral access sites (e.g., back of the hand, wrist, forearm, antecubital fossa) or whether body habitus plays an important role.

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KEY WORDS access site, adenosine, coronary intervention, FFR, fractional flow reserve