UPDATES IN CARDIOLOGY

Thresholds for arterial wall inflammation quantified by 18 F-FDG PET imaging – Implications for Vascular Interventional Studies

Atherosclerosis is a chronic, low-grade inflammatory disease of the arterial wall that causes myocardial infarction and stroke. Arterial wall 18F-FDG uptake mirrors inflammatory activity in atherosclerosis; inflammatory cells consume large amounts of glucose in comparison with other plaque cells, resulting in 18F-FDG accumulation. 18F-FDG positron emission tomography (PET) can identify plaque inflammation as a surrogate endpoint for vascular interventional drug trials. In addition, arterial 18F-FDG uptake is higher in morphologically unstable plaques and predicts future vascular events.

In this study, considering 18F-FDG uptake in the arterial wall of healthy control subjects as physiological, they determined the 90th percentile for arterial wall inflammatory activity using several commonly reported PET endpoints.18F-FDG PET/CT of the carotid arteries and ascending aorta was performed in 83 subjects (61 +/- 8 years) comprising 3 groups: 25 healthy controls, 23 patients at increased CVD (cardiovascular disease) risk (Framingham risk score >10%), and 35 patients with known CVD(experienced myocardial infarction, transient ischemic attack, stroke, or carotid artery atherosclerosis >12 months before PET imaging). All healthy control subjects had a value of 0 for coronary artery calcium score. Exclusion criteria for all subjects were age <40 years, diabetes mellitus, or inflammatory or malignant disease.18F-FDG uptake was assessed in: 1) the carotids starting from 1 slice caudal to the carotid bifurcation downwards; and 2) in the aorta from 1 slice cranial to the pulmonary arteries upwards, per standard methods. From each region of interest (ROI), standardized uptake values (SUVs) were read. SUV represents 18F-FDG activity adjusted for 18F-FDG dose, corrected for decay, and divided by body weight.

All 18F-FDG uptake metrics were significantly different between healthy and diseased subjects for both the carotids and aorta. Thresholds of physiological 18F-FDG uptake were derived from healthy controls using the 90th percentile of their target to background ratio (TBR) value (TBRmax); whole artery TBRmax is 1.84 for the carotids and 2.68 in the aorta. These were exceeded by >52% of risk factor patients and >67% of CVD patients. Reproducibility was excellent in all study groups (intraclass correlation coefficient >0.95). Using carotid TBRmax as a primary endpoint resulted in sample size estimates approximately 20% lower than aorta.

After whole artery metrics, the most-diseased segment TBR was recorded as the mean of 3 adjacent slices with the highest arterial maximum standardized uptake value (SUVmax). In the active segment analysis, slices with 90th percentile of their TBR (TBRmax) values above a pre-defined cutoff level (either >/=1.60, </=1.80, or >/=2.00 for the carotid arteries; >/=2.40, </=2.60, or </=2.80 for the aorta) were considered active, whereas noninflamed segments were excluded.

Whole artery 18-FFDG in the carotids and aorta, expressed as SUVmax, showed a gradual increase from healthy to disease subjects. Using a cutoff of TBR >/=1.60 for the carotids, 48% of the healthy control subjects had at least 1 active slice compared with 96% and 100% of the patients at increased risk for or with known CVD, respectively. With cutoffs >/=1.80 or >/=2.00, the number of healthy control subjects with at least 1 active slice in the carotids decreased substantially. Whereas the %active slices remained significantly different between groups, the TBRactive slices did not

In contrast to the carotids, a much larger proportion of the subjects had active aortic walls. With a cutoff of >/=2.40, 88% of the healthy control subjects had at least 1 active slice; however, the TBRactive slices and %active slices were not distinct between groups. With the active definition at >/=2.60 or >/=2.80, more than one-half of the healthy control subjects still had active segments. For the highest cutoff, TBRactive slices was significantly different between groups ($p = 0.015$).

The present study showed that SUVs and TBRs were consistently higher in the aorta compared with the carotids. This is relevant when applying an "index vessel approach" to drug trials because, in 80% of subjects, the index vessel will originate from the aorta. This might be suboptimal, as we also demonstrated that aortic TBR as endpoint requires a larger sample size to detect drug efficacy. Taking into account that the published drug-induced TBR changes have been

relatively small (ranging between 5% and 15%), the optimal choice of endpoint vessel is important.

The use of the carotid artery as a readout vessel holds the strongest biological validation linking the 18F-FDG signal and inflammation to recommend it. Therefore, they suggest that if the index vessel approach is not used, the carotid artery is best validated as primary readout vessel.

Previously, histological carotid plaque studies demonstrated the correlation between plaque rupture and inflammation; Tawakol et al. were the first to link plaque macrophages ex vivo to plaque inflammation in vivo, demonstrating a linear relation between macrophage content and 18F-FDG uptake in plaques of 17 patients scheduled for carotid endarterectomy. Carotid plaques with a macrophage area of <5% had low TBR values, whereas inflamed carotid plaques with macrophage areas >5% had carotid TBRs between 1.80 and 2.40 (25th and 75th percentiles). Instead of histology-based approaches, they classified arterial wall inflammation using population-based data by regarding the 90th percentile of 18F-FDG uptake metrics in healthy controls as a natural threshold.

What regards the clinical importance, for interventional studies, 18F-FDG PET can help to identify subgroups with inflammation above the physiological range and can provide reproducible measures of drug action. The majority of patients with known CVD have increased inflammatory activity in 1 or more arteries, despite standard-of-care treatments, including statin use in >80%. This residual inflammatory activity suggests the potential for further anti-inflammatory strategies in CVD patients and results of large-scale studies of such intervention are expected. Nevertheless, because of the considerable overlap of 18F-FDG values between healthy control subjects, those at increased CVD risk, and patients with known CVD, it is uncertain whether 18F-FDG PET imaging is capable of identifying individual patients most likely to benefit from new therapies.

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Mitral regurgitation in patients with hypertrophic obstructive cardiomyopathy – Implications for concomitant valve procedures

Mitral valve (MV) leaflets have an important role in the pathophysiological process of left ventricular (LV) outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy (HOCM). Successful septal myectomy has had proven that eliminates or ameliorates SAM of the MV, thus improving associated MR in most patients. Altough the controversy regarding the optimal surgical strategy for patients with HOCM and significant MR related to SAM of the leaflets continues.

The indication to use a direct mitral leaflet procedure in addition to myectomy is based largely on surgeon experience and speculation that isolated myectomy will be inadequate to resolve the SAM. This study wanted to trace indications and suitable operative strategy for mitral regurgitation (MR) in patients with HOCM and has the following aims: 1) how frequently additional procedures are necessary in patients who have SAM-related MR and what is the outcome of septal myectomy alone in such patients; 2) what MV problems require direct repair or replacement in addition to septal myectomy; and 3) when direct MV procedures are necessary, what are the outcomes of valve repair versus valve replacement.

From January 1993 to May 2014 at Mayo Clinic in Rochester, Minnesota, a total of 2,107 septal myectomy operations performed in adults were retrospectively reviewed. Patients with prior MV operation and apical hypertrophic cardiomyopathy were excluded. Overall, 2.004 operations were performed in 1.993 patients (56% men; age at surgery: 53.6 +/- 14.4 years). Before myectomy, MR severity determined by transthoracic Doppler echocardiography was grade <3 in 852 patients (42.5%) and grade >3 (of 4) in 1,152 patients (57.5%). Regarding clinical status, 1,728 patients (86.7%) were classified as NYHA functional class III or IV because of effort dyspnea, chest pain, or syncope.

Of 2.004 operations, intrinsic MV disease was identified pre-operatively in 99 operations, and each of these patients had MV surgery in conjunction with transaortic septal myectomy. 174 patients (99 with and 75 without preoperative diagnosis of intrinsic MV disease) underwent transaortic septal myectomy and concomitant MV surgery. In the 99 patients with intrinsic MV disease identified preoperatively, 68 (68.7%) had MV repair and 31 (31.3%) had MV replacement. The other 42 patients (2.2% of 1,905) had various indications for MV surgery, including redundant leaflet

tissue thought to contribute to LV outflow tract obstruction, minor clefts in leaflets, and iatrogenic injury to chorda during myectomy or inadvertent injury of MV(n = 12 [0.6%]).

Indications to use CPB included a peak pressure gradient LV-aorta >20 mmHg with provocation, significant residual SAM, or MR with a greater than mild degree of severity. CPB was resumed for additional myectomy when the patient had SAM of the MV and residual LV outflow tract obstruction, with or without MR and regardless of its grade.

The impact of resuming CPB after myectomy: among 174 patients undergoing septal myectomy and concomitant MV surgery, 116 had MV surgery during a single aortic cross clamping and CPB (single CPB group). In the other 58 patients, the aortic cross clamp was removed after initial myectomy, the patient was separated from CPB, and myectomy outcome MV was re-evaluated with intraoperative transesophageal echocardiography and direct pressure measurements and additional septal myectomy or MV surgery was performed on the subsequent CPBs (multiple CPB group). Total bypass time or aortic cross clamp time, post-operative ventilation time, length of intensive care unit stay, and length of hospital stay were the same in both groups. No difference in late survival between the groups was detected.

The change in MR after isolated septal myectomy was semnificant. For 1,830 isolated myectomy operations without MV surgery, there was compared preoperative MR assessed through Doppler echo with that observed before hospital discharge. The percentage of patients with MR grade >/= 3 decreased from 54.3% to 1.7% (p =0.001).

In what concerns MV repair versus replacement at the time of myectoy, of the 174 patients with concomitant MV surgery, 133 (76.4%) underwent MV repair and 41 (23.6%) underwent MV replacement. Survival of all patients who had concomitant MV surgery along with myectomy was generally similar to the expected survival of an age- and sex-matched general U.S. population (p=0.08).

It is important to notice that the present study showes that patients who underwent myectomy and concomitant MV repair had better survival than patients who had concomitant MV replacement. These findings support the large body of evidence showing improved late survival of patients undergoing operation for repair of degenerative MV disease versus MV replacement. Nevertheless, it seems best to proceed with concomitant valve repair whenever possible for patients with MR not corrected with adequate septal myectomy.

In conclusion, most MR related to SAM in patients with HOCM resolves after adequate subaortic septal myectomy, and concomitant MV surgery is rarely required unless the patient has intrinsic MV disease. In the absence of diagnosis of intrinsic MV disease, direct MV surgery for SAM and related MR can be safely avoided through the strategy of initially performing adequate myectomy, re-evaluating the result with intraoperative transesophageal echocardiography, and proceeding with any necessary additional MV procedures during a subsequent period of CPB. When MV surgery is required, late outcome is better with MV repair than with replacement.

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Does the routine availability of CT–derived FFR influence management of patients with stable chest pain compared to CT angiography alone? The FFRCT RIPCORD Study

In the assessment of patients with chest pain suspected to be caused by CAD (coronary artery disease), physicians have several possible diagnostic options, and the ideal one would be noninvasive, and it would search for anatomic evidence of coronary disease, evidence of myocardial ischemia, or both.

Recently, using sophisticated image assessment, computational fluid dynamics, and computer modeling, it has become possible to model FFR from the data obtained from CTA, a technique known as computed tomography–derived fractional flow reserve (FFR-CT). This technique does not need for additional radiation exposure or medication and is significantly superior to that of CTA alone, mainly because CTA cannot accurately predict whether a lesion is associated with ischemia. Currently, ICA (invasive coronary angiography) with FFR is the only test that can achieve combined anatomic and physiological assessment.

A series of validation studies have assessed the diagnostic accuracy of this technique, including most recently the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial, which demonstrated the superior accuracy of CTA plus FFRCT versus CTA alone, using an invasive FFR </= 0.8 as the reference.

This study sought to determine the effect of adding computed tomography derived fractional flow reserve (FFRCT) data to computed tomography angiographic (CTA) data alone for assessment of lesion severity and patient management in 200 patients with chest pain. The cases were chosen to reproduce the methodology of the invasive RIPCORD study. The secondary aim was to assess whether the findings from the original invasive RIPCORD study could be reproduced using noninvasive angiography and FFRCT.

200 patients underwent invasive angiography for clinical reasons, and FFR was performed in at least 1 vessel with diameter >/= 2 mm and diameter stenosis >/= 30%. All patients also underwent CTA within 60 days before invasive angiography, and FFRCT data were derived from the dataset using a methodology previously described.

In each case, 3 experienced interventional cardiologists who had access to the expert report generated for clinical reasons, assessed the CT angiogram. They then recorded the location and severity of any coronary stenosis, specifically taking into account whether the lesion was anatomically "significant," by consensus on the basis of visual assessment and the standard expert report.

Then, assuming that each patient was suitable for any 1 of 4 management options: 1) optimal medical therapy (OMT) alone; 2) PCI + OMT; 3) coronary artery bypass graft + OMT; or 4) more information about ischemia required—they committed to 1 option by consensus. Once this decision was made, the FFRCT data were revealed for the case, and the 3 cardiologists were again asked to decide on a management plan, choosing from 1 of 4 options. The vessels that were considered to be "significant" according to whether they were ischemic by virtue of the FFRCT result (cutoff value </= 0.80) also were recorded.

In this study population, a stenosis was considered "significant" if it had diameter narrowing >50%. From the site-read cases, 8 (4%) reported as having no significant obstructive disease on CTA had obstructive disease on quantitative coronary angiography on the invasive catheterization. Of these 8 cases, 7 (87.5%) had a negative FFRCT, and 1 (12.5%) had a positive FFRCT. From the site-read cases, 94 (47%) reported as having significant obstructive coronary disease on coronary CTA were later found to have no obstructive disease on quantitative coronary angiography on the invasive catheterization. Of these 94 cases, 57 (60.6%) had a negative FFRCT, and 37 (39.4%) had a positive FFRCT.

The effect of FFR-CT on the treatment management, after FFR-CT data became available, was significant. A change in the allocated management category on the basis of CTA alone was seen in 72 cases (36%). Of the 38 patients originally allocated to the "more information required" category on the basis of CTA alone, 10 (26%) were reallocated to revascularization and the remaining 28 (74%) to OMT. Of the 87 cases originally thought to require PCI on the basis of CTA alone, 26 (30%) were reallocated to OMT on the basis of no ischemic lesion detected by FFRCT, and in 16 (18%) the target vessel(s) for PCI was changed on the basis of FFRCT. These changes resulted from a discordance between the CT angiographic and FFRCT assessments of lesion severity. In 366 vessels (63.4% of the total) categorized as having CT angiographic severity </=50% diameter stenosis, FFRCT was >0.80 in 17 (4.6%). In contrast, FFRCT was negative for ischemia (i.e., >0.80) in 13 of 44 cases (29.5%) graded as having diameter stenosis >90% and in 38 of 83 cases (45.8%) graded as having diameter stenosis of 71% to 90%.

This study proved the hypothesis that the management of patients with stable chest pain on the basis of CTA results alone would be significantly different if FFRCT data were available. Also, advances in the technology related to CTA have been associated with lower radiation exposure and higher resolution, although diagnostic quality remains compromised in certain patient groups, including those with arrhythmias, patients with high levels of coronary artery calcification, and the obese.

This study demonstrates a proof of concept that the availability of noninvasive FFRCT has a substantial effect on the ability to identify significant CAD and therefore on the management of patients with stable chest pain compared to CTA alone. This finding mimics the observation seen using invasive ICA and FFR in the RIPCORD study. Further studies are required to assess whether FFRCT may represent a candidate as a noninvasive diagnostic and management screening test for patients with stable chest pain.

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Hyperkalemia in Heart Failure

Disorders of potassium homeostasis can be life threatening because of the associated risk for arrhythmias

and conduction system abnormalities. Generally, a serum potassium level higher than 5.0 mmol/l is defined as hyperkalemia. Among patients hospitalized for any cause, the prevalence of hyperkalemia has been estimated at 1% to 10%. Patients with chronic kidney disease (CKD), heart failure (HF), and diabetes mellitus and those using renin-angiotensin aldosterone system inhibitors (RAASi) are at 2 to 3 times higher risk for hyperkalemia. Angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) have proven benefit in HF treatment of this patients, but they are also at high risk for hyperkalemia. Thus, many patients in need for these therapies are unable to tolerate them, or if these medicines are prescribed, they are prescribed at less than optimal dosages. RAASi discontinuation for hyperkalemia represents an undesirable clinical compromise.

The rate of in hospital hyperkalemia associated death in HF patients increased from 0.10 of 1,000 patients in 1994 to 0.39 of 1,000 patients in 2001 ($p < 0.001$)-according to the RALES trial. These data underscore both the importance of hyperkalemia when augmenting RAASi and the need for careful monitoring of electrolytes.

Hyperkalemia risk is increased with concomitant CKD in HF patients. In 105.388 HF patients enrolled in the ADHERE (Acute Decompensated Heart Failure National Registry) study, more than 60% of patients had kidney disease. In patients with CKD, the prevalence of hyperkalemia can be up to 20% and is associated with the risk of mortality and major adverse cardiovascular events and discontinuation of RAASi .Also, most trials excluded patients with moderate or severe CKD, which is common in HF, especially at advanced stages.

The use of effective and safe potassium binders now provides an opportunity to assess RAASi in such patients. In the meantime, several steps can be taken to attempt RAASi therapy in such patients. First, potassium supplements or salt substitutes containing potassium should be stopped or used judiciously under supervision. It may be preferable to use lower doses of both RAASi and MRAs rather than higher doses of one and not to use the other class of drugs altogether. In case of worsening renal function, the risk of hyperkalemia and the rate of decline in renal function should be assessed. There are no specific guidelines, but generally, ACEi or ARB doses may be reduced or stopped, either temporarily or permanently, with estimated glomerular filtration rate (eGFR) <15 to 30 ml/min, whereas they can be used in dialysis patients with careful monitoring. Currently, MRAs are contraindicated in patients with eGFR <30 ml/min.

Current management of hyperkalemia

Emergent management: In patients with electrocardiographic changes and/or potassium levels >7.0 mmol/l, intravenous calcium is administered to prevent arrhythmia. To rapidly lower potassium levels, insulin and beta-2 adrenoreceptor agonists are used to redistribute potassium from the extracellular to the intracellular space; however, this is a temporary measure.

Intermediate management: Dialysis can be used in patients with poor kidney function or in those who are unresponsive to other treatments. In patients with CKD and metabolic acidosis, sodium bicarbonate therapy is an effective strategy to minimize increases in the potassium concentration. Loop diuretic agents are effective in excretion of potassium by the delivery of sodium in the collecting duct.

Maintenance: In addition to dietary potassium intake restriction, lowering the dose of drugs that impair potassium excretion or administering them every other day or totally discontinuing them is often needed. This should include a review of all dietary and herbal supplements and salt substitutes as well. Potassium-binding resins can also be used; however, until recently, the only approved ion exchange resin was sodium polystyrene sulfonate, which was not well tolerated and may cause colonic necrosis and intestinal injury.

New treatments for hyperkalemia

Sodium polystyrene sulfonate has significant limitations for chronic use and has not been evaluated in large randomized trials. Its use in HF is limited, as it may worsen edema by exchanging sodium for potassium ions. In addition, it is poorly tolerated and associated with severe and even fatal gastrointestinal complications. In a small single-center randomized controlled trial in 33 outpatients with CKD and mild hyperkalemia (5.0 to 5.9 mmol/l), a sodium polystyrene sulfonate dosage of 30 g orally once daily for 7 days achieved normokalemia in 73% of the patients versus 38% of patients in the placebo group.

Patiromer, is a nonabsorbed polymer designed to bind potassium in the gastrointestinal tract and reduce serum potassium levels, which was recently approved by the U.S. FDA. Patiromer predominantly uses calcium as the exchange cation, instead of sodium. Patiromer is administered as once daily with food and promotes

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ionization of the polymeric potassium-binding moiety under pH conditions present along the extent of the gastrointestinal tract, predominantly in the colon.

Sodium zirconium cyclosilicate (ZS-9) is an inorganic, orally administered potassium binding compound that has recently been investigated in phase II and III clinical trials. ZS-9 is administered as a once-daily dose, and its physiological ion channels filter ions on the basis of their differing diameters. ZS-9 has a structure that mimics physiological potassium channels and selectively captures potassium cations. ZS-9 is not absorbed in the gastrointestinal tract and is available as insoluble, free-floating, odorless, tasteless, white crystalline powder. It is an inorganic compound, unlike sodium polystyrene sulfonate, and specifically traps monovalent (potassium and ammonium) over divalent cations (like Ca2+ or Mg2+). Because it is not systemically absorbed, the risk of systemic toxicity is low.

Effect on aldosterone

Rrenal hypoperfusion in HF activates the RAAS, which increases norepinephrine and angiotensin II, causing vasoconstriction and release of aldosterone through alpha-adrenergic and angiotensin II type I receptors. RAAS stimulation contributes to salt and water retention, renal potassium excretion, and activation of the sympathetic nervous system. RAASi inhibit aldosterone, resulting in decreased potassium excretion. Weir et al. analyzed the effect of patiromer on serum aldosterone levels in patients with CKD in the OPAL-HK trial. A reduction in plasma aldosterone levels and in the urine aldosterone-to creatinine ratio at 4 and 8 weeks of patiromer use was observed. Similarly, a reduction in systolic (SBP) and diastolic (DBP) blood pressure and in the urinary albumin to creatinine ratio was also observed. Data from HARMONIZE showed a 30% reduction in serum aldosterone with ZS9 after 28 days of treatment. It is important, in the future, to study the clinical relevance of this finding.

Effect on blood pressure

Treating hyperkalemia with patiromer, in addition to maintenance of RAASi therapy, may improve blood pressure control. A subgroup analysis from the AMETHYST-DN trial in a cohort of 79 of 306 patients with diabetic kidney disease and resistant hypertension (defined as systolic blood pressure [SBP] >140 mmHg in 4 or more classes of antihypertensive drugs), who were treated with patiromer for hyperkalemia and continued with RAASi therapy, showed decreases in SBP and diastolic blood pressure (DBP) of -18+/- 17 mmHg and -9.0+/- 13 mmHg, respectively, at the end of 52 weeks of therapy. The interim analysis of the 711 patients enrolled in an ongoing ZS-9 study (ZS005) to evaluate the long term (52 week) efficacy and safety of ZS-9 showed hypertension in 7% (48 of 684) patients. More prospective data are needed to further explore the effect of patiromer on blood pressure.

Future direction

According to HF guidelines, MRAs should not be used in patients with eGFR<30 ml/min or serum potassium levels >5.0 mmol/l. This leads to the exclusion of a significant group of HF patients (18% to 40%) with reduced ejection fraction who are not prescribed MRAs . Similarly, the use of ACEi or ARBs is seen only in 55% to 63 % of patients with CKD in primary care; Recent discovered drug therapy will provide the opportunity to study those groups of patients who were excluded from clinical trials due to hyperkalemia. Although subgroup analysis of HF patients supported the ability of these agents to continue RAASi use in HF, further studies of up-titration to optimal dosing of RAASi in HF are needed.

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