REVIEW ARTICLE—HERMANN BLUMGART AWARD

From Myocardial Blood Flow to Receptor Imaging with PET: Hermann Blumgart Award Lecture 2018

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Abstract

Cardiac PET with assessment of myocardial perfusion and flow quantification with cardiovascular risk prediction in clinically-manifest and subclinical CAD has evolved as a mainstay in the clinical decision-making process. In this respect, cardiovascular PET continuous to expand its clinical scope with assessment of infiltrative-inflammatory cardiac disease, vasculitis, and device infections. Conversely, PET flow quantification for the identification and characterization of coronary circulatory dysfunction in conjunction with various biomarkers has provided unique "in vivo" insight into early functional stages of the CAD process that may complement or even guide experimental studies that investigate direct cause-effect relationships. Further, emerging radiotracer probes with PET may probe non-invasively myocardial receptor expressions, such as cannabinoid type 1 receptors that may play a role in heart failure development in obesity and/or diabetes mellitus deserving further clinical evaluation.

Keywords: Coronary circulatory dysfunction, Inflammation, Myocardial blood flow, Myocardial receptor imaging, PET
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The Hermann Blumgart Award is the highest award and honor bestowed by the Cardiovascular Council (CVC) of the Society of Nuclear Medicine and Molecular Imaging (SNMMI). The election by the Board of Directors of the CVC is based on criteria of both scientific contributions to the field of cardio-vascular nuclear medicine and service to the Council. Dr. Thomas H. Schindler from the Washington University in St. Louis, Missouri, USA was the 2018 Hermann Blumgart Award recipient of the SNMMI (Figure 1a). Hermann L. Blumgart (1895–1977) was a pioneer in cardiovascular nuclear medicine who was first to perform diagnostic procedure using radioactive indicators in man in 1925 [measurement of arm-to-arm circulation times using "radium C" (Bi-214)] (Figure 1b), while he also developed the instrumentation for in-vivo detection, the so called Blumgart-Yens modified cloud chamber. He is commonly regarded as "father of diagnostic nuclear medicine" with a highly perceptive and original mind, who described himself as a "Teacher, Physician, Administrator and Scientist" (Clin Cardiol. 1991; 15: 308–311). This review reflects the 2018 Blumgart Award Lectures addressing the emerging fields of cardiovascular positron emission tomography (PET) imaging, held at the annual meeting in Philadelphia, Pennsylvania, USA, 24th June, 2018.

Experimental and clinical investigations stress the critical role of the functional integrity of endothelium-dependent coronary vasomotor function in conferring anti-atherosclerotic and anti-thrombotic effects (1). Vice versa, an impairment of coronary vascular function represent a pro-atherosclerotic state that carries substantial diagnostic and prognostic information (1–4). Until a decade ago, the assessment of endothelium-and endothelium-independent coronary vasomotor function was initially limited to symptomatic patients undergoing invasive coronary angiography (5). Computer-based, quantified analysis of changes in epicardial diameter with and/or alterations in intracoronary Doppler-measured flow velocity in response to intracoronary infusion of acetylcholine were commonly applied to specifically assess

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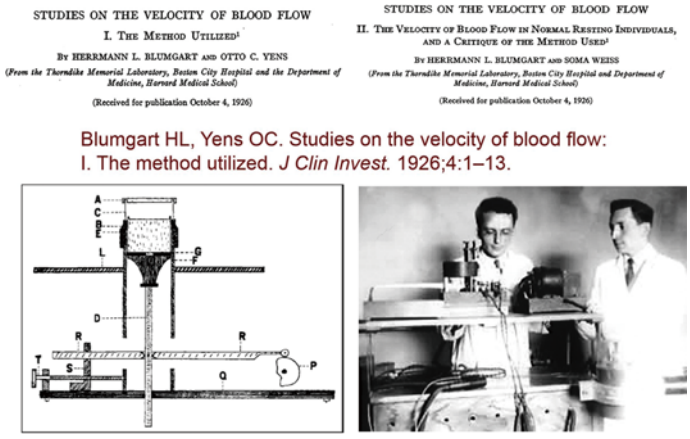


(**b**)

Figure 1 2018 Blumgart Award Ceremony.
a: Award Group Picture.
Pictured left to the right: Vasken Dilsizian, MD, SNMMI President; Panithaya Chareonthaitawee, MD, CVC President, Thomas H. Schindler, MD, Blumgart Award Recipient; and Robert J. Gropler, MD, CVC Immediate Past President.
b: Hermann Blumgart Publications and Illustration of the Studies on the Velocity of Blood Flow.
Pictured left to the right: Otto C. Yens and Hermann L. Blumgart.

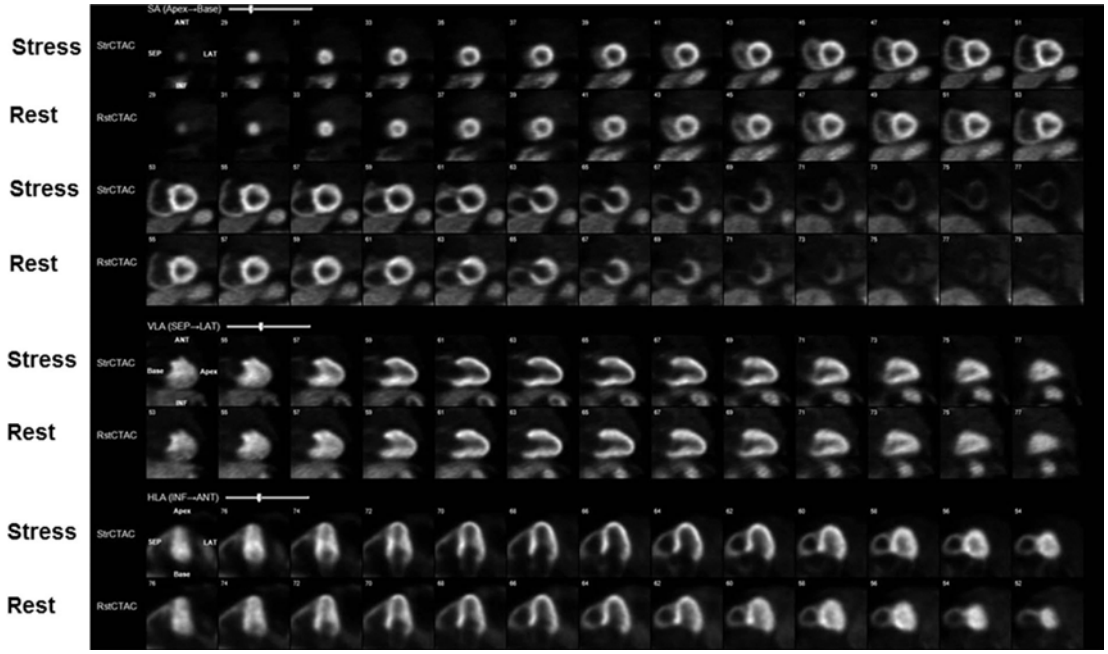
receptor-mediated release of endothelium-derived nitric oxide and, thus, endothelium-dependent vasomotion of the epicardial artery and coronary arteriolar vessels, respectively. Conversely, endothelium-independent or vascular smooth muscle cell response of the epicardial artery was commonly determined after intracoronary application of nitroglycerine as nitric oxide donor, while the use of substances like papaverine or adenosine caused a vascular smooth muscle cell relaxing effect at the site of the coronary arteriolar resistance vessels leading to predominant endothelium-independent coronary flow increases (5). Given the invasive nature of coronary vasomotor function assessment, a more widely used application for cardiovascular risk stratification and gain in mechanistic insights of the CAD was not possible.

With the advent of cardiac positron-emission-tomography (PET) and tracer-kinetic modeling, the non-invasive quantification of myocardial blood flow in milliliter/gram/minute (mL/g/min) became possible (1). The non-invasive approach of PET-measured myocardial perfusion in conjunction with MBF quantification opened new avenues in the detection of subclinical and clinically manifest CAD, cardiovascular risk stratification, and mechanistic insights in early and functional stage of developing CAD (Figure 2) (1, 5–7). This review aims to provide a concise overview on the promise of cardiac PET/CT flow quantification in the non-invasive detection of coronary circulatory dysfunction and outcome prediction, contribution to mechanistic insights into vasomotor dysfunction, monitoring of treatment responses, and its increasing application in assessing infiltrative-inflammatory cardiac disease, vasculitis, and device infections, and the emerging field of myocardial cannabinoid type 1 receptor imaging.

PET-determined parameters of coronary circulatory dysfunction and outcome prediction

For the assessment of coronary circulatory function, PET-measurements MBFs at rest and its response various forms of vasomotor stress can be conducted (1, 5, 8, 9). The latter may include bicycle exercise, dobutamine stress, sympathetic stimulation with cold pressor testing (CPT), vascular smooth muscle cell relaxation at the site of the coronary arteriolar vessels, or heterogenous responses of MBF in more apical and more basal regions of the left ventricle as a possible non-inavsive index of epicardial vasomotion.

It is important to note that vascular smooth muscle cell-relaxing agents such as regadenoson, dipyridamole, or adenosine are commonly applied intravenously to lower the resistance to flow at the site of the coronary arteriolar vessels that in the normal setting manifests in a maximal or sub-maximal hyperemic MBF increase (5). Of note, inhibition of the endothelial nitric-oxide-synthase by intravenous infusion of L-NG-monomethyl arginine significantly reduces adenosine-induced MBF increases by 20–25% as measured with PET (5). Thus, pharmacologic-stimulated increase in hyperemic coronary flow causes a flow-mediated and thus endothelium-dependent vasodilation of the upstream coronary arterial segments that contributes by 20–25% to the global hyperemic MBF increase (5). The flow and nitric oxide (endothelial) mediated vasodilatory component may also explain the independent predictive value of impaired hyperemic MBF and MFR for future cardiovascular events (2, 3, 10, 11). Since hyperemic MBFs during pharmacological vasodilation are mainly related to the relaxation of the vascular smooth muscle cells, they provide information on predomi-



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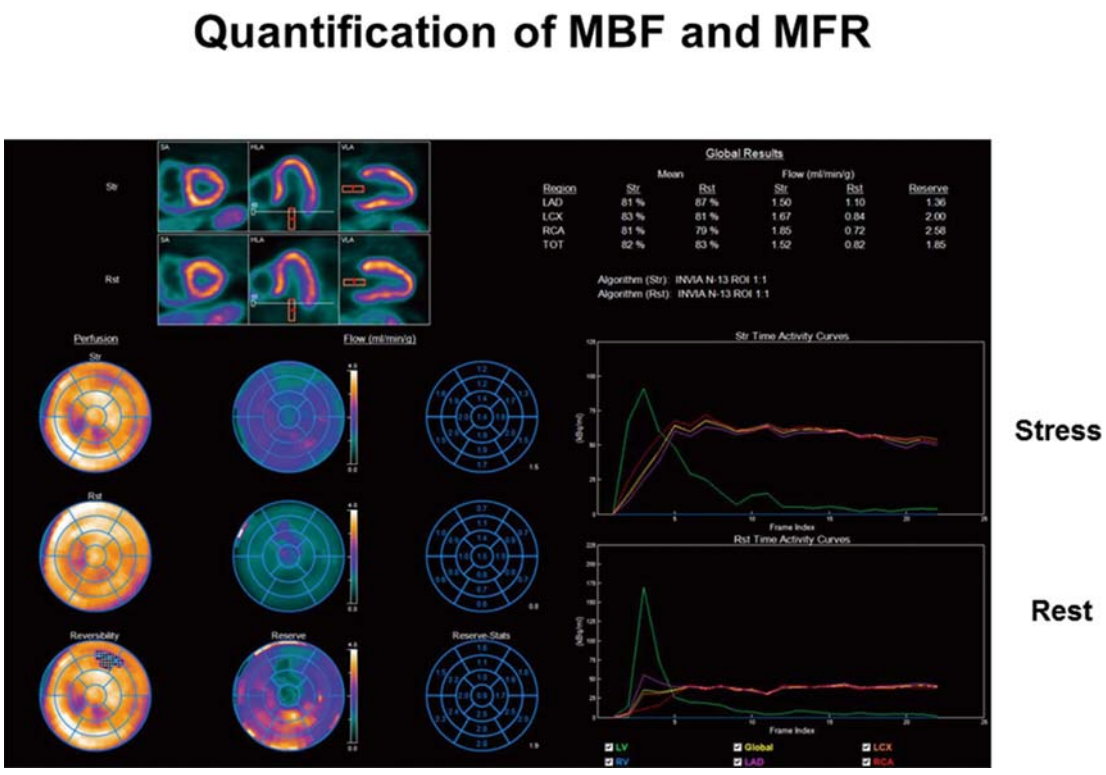


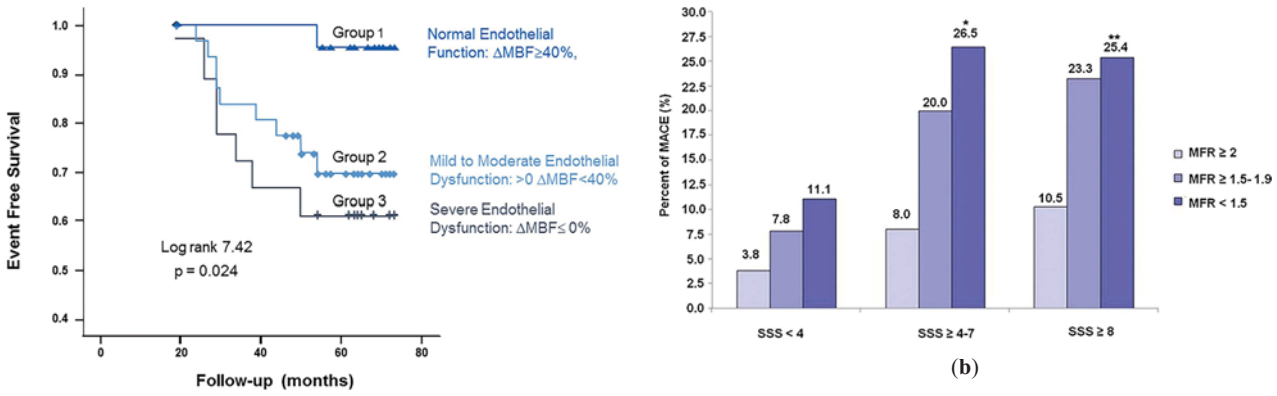
(**b**)

Figure 2 Stress-Rest ^{13}N-ammonia PET/CT.

Myocardial Perfusion and MBF Assessment in an Individual with Morbid Obesity.

a: Stress and rest ^{13}N-ammonia PET images of the heart in short-axis, vertical long-axis, and horizontal long-axis slices are shown from a 68-year-old woman with a body mass index (BMI)≈48kg/m^2, type 2 diabetes mellitus, dyslipidemia, and arterial hypertension, presenting with chest tightness during minor exercise and daily activities. The stress-rest images demonstrate widely homogenous radiotracer uptake and, thus, normal ^{13}N-ammonia uptake of the left ventricle.

b: Global and regional myocardial blood flow quantification (MBF) and myocardial flow reserve (MFR) calculation with ^{13}N-ammonia PET/CT and tracer kinetic modeling. The summarized quantitative data denote globally reduced hyperemic MBFs (<1.80 ml/g/min) and myocardial flow reserve (MFR<2.0). Wall motion analysis with gated-PET signified normal wall motion and thickening of the left ventricle at peak stress and at rest associated with global LVEF of 53% and 56%, respectively (not shown). Thus, there is no evidence of ischemia during pharmacologic vasodilator stress, while the reductions in global hyperemic MBFs and MFR of the left ventricle signifies coronary microvascular dysfunction that may account for the reported angina symptoms of the patient.



(a) (b)

Figure 3 Coronary Circulatory Function and Prognosis.
a: Coronary Endothelial Vasomotor Function and Outcome.
Kaplan-Meier analyses in cardiovascular risk individuals with normal coronary angiograms undergoing assessment of coronary endothelial vasoreactivity by means of positron emission tomography (PET)-determined myocardial blood flow (MBF) response to cold pressor test (CPT) and at rest. An impairment of endothelium-related MBF challenge to sympathetic stimulation with cold pressor testing is accompanied by a higher risk for cardiac events (during long-term follow-up) as compared with those with normal flow increases; normal (%ΔMBF≥40%), impaired (%ΔMBF>0% and <40%), and decreased (%ΔMBF ≤0%). (With kind permission from reference (2))
b: PET-Measured MFR and Outcome.
Within subgroups of summed stress score (SSS) for different levels of MFR, at any level of SSS, the prevalence of major cardiac events (MACE) is significantly higher in patients with the lowest MFR (<1.5) when compared to MFR ≥2 among patients with ischemia. *P=0.028 for SSS≥4–7 and MFR<1.5 vs. MFR≥2. **P=0.002 for SSS≥8 and MFR<1.5 vs. MFR≥2. (With kind permission from reference (3))

nantly endothelium-independent microcirculatory dysfunction that sometimes is also reported as total integrated coronary circulatory function (1, 5). PET-determined MBF during sympathetic stimulation with CPT and at rest is commonly performed for research purpose in order to assess specifically the vasoreactivity of the coronary endothelium in various cardiovascular risk setting and to monitor the success of preventive medical care on coronary endothelial dysfunction (5, 12). Since PET-determined myocardial perfusion and flow during pharmacologic vasodilation implies the assessment of hemodynamically obstructive CAD, microvascular dysfunction or both, it is routinely applied in the clinical management of patients with suspected or known CAD. In clinical routine, the distinction between coronary endothelial-independent versus -dependent flow response is not relevant as the PET-determined total integrated coronary flow response is indeed an independent predictor of outcome in cardiovascular risk individuals with or without obstructive CAD (1–3, 10, 13–15). We gave a first example, however, that PET assessment of coronary endothelial dysfunction is associated with a worsened cardiovascular outcome (Figure 3a) (2). Seventy-two individuals with cardiovascular risk factors but normal invasive coronary angiogram underwent MBF assessment with ^{13}N-ammonia PET at rest and during CPT to non-invasively probe endothelium-dependent coronary flow increases. After a mean follow-up period of 66±8 months, cardiovascular risk individuals with a diminished increase in MBF to CPT and its MFR had a higher risk for cardiovascular events than in those with normal flow increases during sympathetic stimulation (2). Notably, the cardiovascular event rate increased in function of the severity of coronary endothelial dysfunction. Subsequently, Herzog et al. (10) demonstrated than normal stress perfusion and MFR findings, as determined with ^{13}N-ammonia PET, signified a so called "warranty" period of event-free survival for about 3–4 years when compared to those with abnormal reductions in MFR. Further, also in those patients with stress-related and regional perfusion deficit, indicative of obstructive CAD, the concurrent assessment of microvascular dysfunction signified incremental predictive value for cardiovascular outcome. Such predictive value of PET-determined reductions in hyperemic MBF or myocardial flow reserve on cardiovascular outcome was also confirmed in a large cohort of 704 consecutive patients with suspicion for or known CAD (3) and in a total of 2, 783 patients with suspicion or known CAD undergoing stress-rest ^{82}Rubidium PET myocardial perfusion imaging (11) (Figure 3b). The incremental value of reduced MFR, reflecting microvascular dysfunction, for cardiac death were also demonstrated for specific risk populations such as in women, in diabetes mellitus, cardiometabolic disease, obesity, chronic kidney disease, hypertrophic obstructive cardiomyopathy, cardiac allograft vasculopathy, ischemic or idiopathic cardiomyopathy, or in heart failure with preserved left ventricular ejection fraction (HFpEF) (4, 14, 16) .

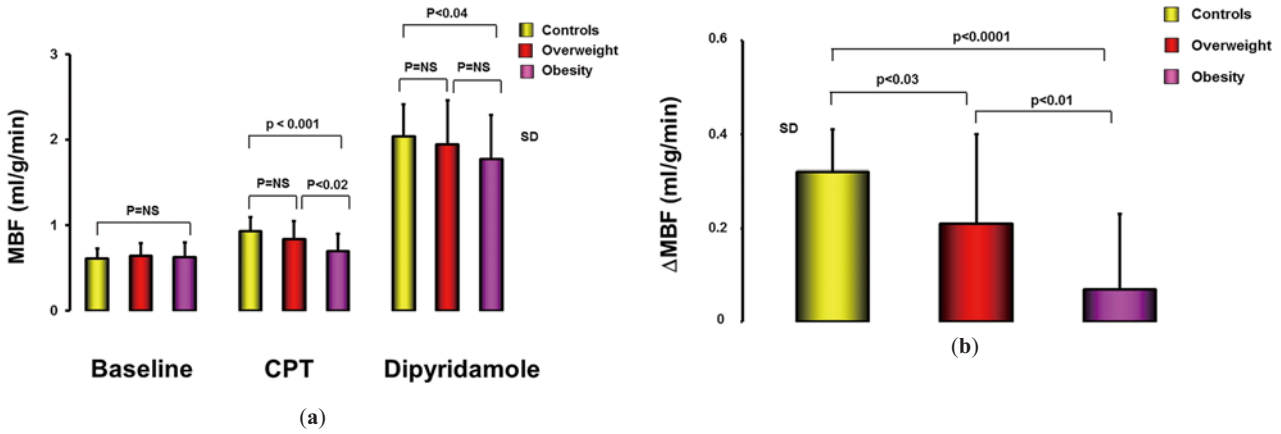


Figure 4 Myocardial Blood Flow and Increasing Body Weight.
a: displays myocardial blood flow (MBF) at rest, during cold pressor testing (CPT), and during pharmacologic vasodilation with dipyridamole for normal weight controls (BMI<25 kg/m^2), overweight (BMI≥25 to 30 kg/m^2) and obese (BMI>30 kg/m^2) individuals. Hyperemic MBFs were non-significantly less in overweight than in controls, while lowest in obesity. As can be appreciated in (**b**), there is a progressive decrease of endothelium-related MBF during CPT (ΔMBF) from control, to overweight and obesity. (With kind permission from reference (18))

Mechanistic insights in regulation of coronary circulatory function

The PET assessment of myocardial flow responses to various forms of vasomotor stress such as with sympathetic stimulation by means of CPT and pharmacologic vasodilation has also emerged as a unique approach to gain *in vivo* mechanistic insights underlying early functional stages of the initiation and development of CAD (5, 6), that may even contrasting experimental or clinical flow investigations in the peripheral circulation (1). Such observations may suggest complex mechanisms that may lead to disturbances of coronary endothelial dysfunction. For example, we could demonstrate a heterogenous responses in endothelium-related MBFs during CPT to short- and long-term antioxidant intervention with vitamin C in patients with different coronary risk factors such as smoking, arterial hypertension and hypercholesterolemia (6). Such "*in vivo*" findings by PET imaging (6) may contrast experimental investigations that proposed increases in reactive oxygen species as main common pathway underlying endothelial dysfunction (17) and, thus, may suggest rather complex mechanism which may account for abnormalities in coronary circulatory function. In recent years, PET flow studies have also focused on the assessment of microvascular function in individuals with obesity commonly associated with insulin resistance syndrome and inflammatory state (7, 18). Since obesity has been increasingly appreciated to represent a risk factor for cardiovascular morbidity and mortality (19), it has triggered a large array of experimental and clinical studies exploring the exact mechanisms underlying the early initiation of abnormalities in coronary vasomotor function commonly seen as functional precursor of the CAD process (18, 20–24). The vascular injury caused by cardiovascular risk factors may be initially confined to the vascular endothelium but may also expand to the vascular smooth muscle cell layer in function of increasing detrimental effects of risk factors (18). This is reflected by findings of coronary vascular function in healthy individuals with increasing body weight (18). Disturbance of coronary circulatory function in individuals with increasing body weight advances from diminished endothelium-dependent MBF response to CPT in overweight to a reduction of the predominantly endothelium-independent hyperemic MBFs during dipyridamole stimulation in obesity (Figure 4). Notably, the assessment of coronary circulatory function in individuals with increasing body weight but otherwise healthy could indeed demonstrate that obesity was independently associated with a coronary dysfunctional state (18). Thus, apart from well-known effects the insulin-resistance syndrome and inflammation on coronary circulatory function, these findings with PET flow studies yielded first evidence that mediators originating from the adipose tissue may have direct effects on vascular function in obesity. Such mediators released from the adipose tissue or so called adipocytokines such as leptin, adiponectin, or ghrelin altering coronary circulatory function is an ongoing quest (20). While adiponectin and ghrelin may exerts preventive effects against CAD development by stimulating the release of endothelium-derived and atheroprotective nitric oxide, it remains controversial for leptin (5, 18). Given these contrasting findings, PET flow studies in obese individuals unraveled a positive relationship among leptin plasma levels and endothelium-related MBFs to CPT ($r=0.37$, $p<0.036$). Thus, obesity related increases in leptin plasma levels were associated with relatively higher and maintained endothelium-related MBF increases to CPT suggesting potential beneficial effect of leptin and/or leptin-related but still undetermined factors on

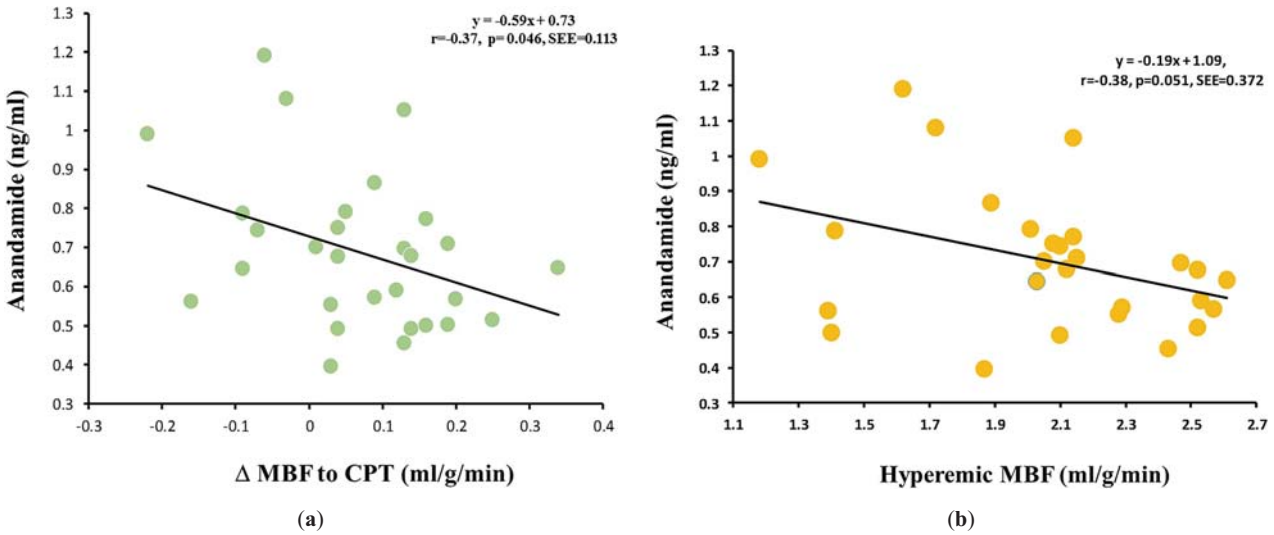


Figure 5 Endocannabinoids and Coronary Vasoreactivity.
Inverse correlation between anandamide plasma levels and change in endothelium-related MBF to CPT (**a**) and hyperemic MBFs (**b**) in obesity, respectively, signifying that increases in endocannabinoids in the circulation are indeed associated with coronary circulatory dysfunction. (With kind permission from reference (21))

coronary endothelial function striving to balance the adverse effects of increases in body weight on coronary circulatory function (18).

In another study with 77 study participants with increasing body weight, increases in endocannabinoids, predominantly released from adipose tissue, were inversely associated with reductions in endothelium-related MBF response to CPT and hyperemic MBFs, respectively (Figure 5) (21). Such findings yielded first direct *in- vivo* evidence that increases in endocannabinoids, such as in anandamide (AEA) and 2-arachidonoylglycerol (2-AG), may mediate adverse effects on coronary endothelium- and smooth muscle cell function in obesity (21). Support comes also from experimental investigation in apolipoprotein E-deficient ($ApoE^{-/-}$) mice (25), in which inhibition of CB1 receptor by rimonabant in the aorta and visceral adipose tissue did lead to reduction in aortic reactive oxygen species production and NADPH oxidase activity paralleled by an improvement in endothelium-dependent vasodilation. Further, increases in endocannabinoids that bind to CB1 and CB2 receptors of the vascular endothelium and smooth muscle cells and activation of both are likely to mediate pro-atherosclerotic effects, such as increases in oxidative stress and vascular adhesion molecules like VCAM-1 expression, monocyte adhesion, and migration into the arterial wall, as experimental *in vitro* studies have outlined (20).

Although PET assessment of coronary circulatory function have convincingly unmasked a cause-effect relationship between the severity of insulin-resistance and functional disturbances of the coronary circulation in non-obese individuals, such relationship may not be that evident any more as other metabolic and hormonal factors may manifest in obesity. For example, elevations of endocannabinoids, like anandamide and 2-arachidonoylglycerol, likely confound directly or indirectly the relationship between insulin resistance and coronary vasodilator capacity in obesity and also type 2 diabetes mellitus (20, 26). Endocannabinoids are produced and released upon demand from the brain, peripheral organs, as well as from the adipose tissue, while their biological effects are mediated via binding with specific G-protein coupled cannabinoid receptors type 1 and type 2 and activation thereof (20). Detrimental effects of increased plasma endocannabinoid levels on coronary circulatory function may indeed overcome reported beneficial effects of leptin and adiponectin on the function of the coronary circulation in obesity (21, 23, 24), favoring the initiation and development of CAD (1). Thus, there is a new concept involving that the adipose tissue may produce and release mediators or adipocytokines with pro- or anti-atherosclerotic effects (e.g. endocannabinoids versus adiponectin) and that the imbalance of these factors is representing the critical integral factor of a disturbance of coronary circulatory dysfunction in obesity (24).

Treatment response and monitoring

Given the evidence that PET-determined abnormal coronary flow response to different forms of vasomotor stress precedes structural alterations of the CAD process (1, 5), it could prove to be useful to personalize preventive medical care and the prediction of treatment efficacy in cardiovascular risk individuals. Instead of standard preventive medical care for cardiovascular risk individuals, the doses of medical pharmacotherapy could be adapted to the MBF responses during vasomotor stress with PET imaging. In some cases, higher

doses of pharmacotherapy may be needed to achieve complete restoration of the hyperemic MBF response and MFR and therefore optimal treatment effect likely to improve patient's cardiovascular outcome (27). In other cases, e.g. doses of beta-hydroxymethylglutaryl coenzyme A reductase inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers or hormone-replacement therapy (1, 28) could be tapered down towards standard treatment for achieving normal flow responses that would lessen potential pharmacotherapy related side effects and thus safety in clinical long-term application. While statins, ACE-inhibitors, and angiotensin II type 1 receptor blockers have been demonstrated to confer direct protection of the vascular endothelium against the detrimental effects of increases in reactive oxygen species as a common final pathway of cardiovascular risk factors, someone would assume that the concurrent increase in hyperemic flows due to improved function of the coronary arteriolar vessels would result into an enhanced flow-related and, thus, nitric-oxide mediated vasodilation of the epicardial conductance artery. The flow-mediated activation of the endothelial nitric-oxide synthase with production and release of nitric oxide from the endothelium into the subintimal space mediates additional and physiologic vascular protection owing to the anti-inflammatory, -oxidative, -proliferative effects of nitric oxide as well as its inhibitory effects on thrombocytes-aggregation and on neutrophil migration into the arterial wall (1). Such an assumption was followed in a more recent glucose-lowering treatment trial assessing coronary circulatory function, coronary artery calcification and carotid intima-media thickness in type 2 diabetes mellitus (27). Twenty-two individuals with type two diabetes mellitus were evaluated for glycemic control with glyburide and/or metformin over a fourteen months follow-up, while seventeen healthy, normal weight individuals without known cardiovascular risk factors served as control group. The anti-diabetic medication related glucose-lowering effect was indeed accompanied by a slowed progression of structural alterations of the arterial wall and an improvement in coronary circulatory function, respectively. In view of these findings, it is intriguing to speculate that an improvement or even normalization of microvascular dysfunction by primary or secondary preventive care for CAD, as demonstrated in numerous PET studies (1), is likely to result into an improved cardiovascular outcome but needing further evaluation in randomized and large-scale clinical trials.

It is important to keep in mind, however, that the CAD develops directly in the coronary arterial wall. This is mirrored by cardiac PET/CT (4, 15, 29) that some patients may have extensive atherosclerotic burden, as reflected by non-contrast CT-determined high coronary artery calcium score, but also normal or high stress flows and MFR. While these patients certainly do not need any procedures for coronary revascularization, they still require initiation and/or intensified control of cardiovascular risk factors with preventive medical care and/or behavioural interventions related to weight, diet and physical activity.

Assessment of infiltrative-inflammatory cardiac disease, vasculitis, and device infections

FDG-PET/CT imaging is increasingly used to identify and characterize different cardiovascular disease entities associated with an inflammatory process (30–32). This includes active-inflammatory cardiac sarcoidosis, myocarditis, large vessel and non-specific vasculitis, and cardiac device infections. FDG-PET/CT may afford the advantage to identify an inflammatory process ahead of morphological alterations, as can be determined with computed tomography or magnetic resonance imaging, and monitor treatment response. In regions with a high prevalence of sarcoidosis in the US, cardiac PET/CT with FDG and perfusion imaging has evolved as mainstay in the detection of cardiac sarcoidosis and in monitoring of the immunosuppressive medical treatment (33, 34). While cardiac FDG-PET has a high sensitivity and specificity for the detection of cardiac sarcoidosis, it is also apt to non-specific and false positive findings in up to 15% that necessitates expert reading and clinical correlation (30, 35). Apart from the visual evaluation of the myocardial FDG uptake, adding the semiquantitative assessment applying the standardized uptake value (SUV) is recommended for achieving a more accurate detection and characterization of cardiac sarcoidosis activity (36). The additional performed whole body or thoracic FDG-PET/CT scans also enable the assessment of active systemic sarcoidosis that may increase the confidence for cardiac findings and provides a comprehensive assessment of systemic sarcoidosis activity (37). More recently, the non-invasive identification of large vessel vasculitis such as Takayasu arteritis and giant cell arteritis and treatment response assessment with FDG-PET/CT has gained increasing clinical interest (38). Similarly, FDG-PET/CT may be suitable for the detection of cardiovascular device infection or its exclusion (31, 39). There are different types of cardiovascular devices such as such as cardiac implantable electronic devices (including pacemakers and defibrillators), prosthetic valves, and left ventricular assist devices (31, 32). Infections may affect extra-cardiac structures of devices, such as the pocket or lead of a pacemaker or defibrillator and the driveline of a left ventricular assist device, or in the intra-cardiac components, such as the prosthetic valve and left ventricular assist device pump or conduit. Applying FDG-PET/CT affords an early identification of cardiovascular device infections such for prosthetic valve endocarditis that may go beyond classical anatomical criteria and methodological difficulties of transesophageal echocardiography and

computed tomographic angiography (31). Depending on the clinical scenario it may be critical to add ^{18}F-FDG-PET imaging to of transesophageal echocardiography and computed tomographic angiography for more definite diagnosis of prosthetic valve endocarditis and other device infections that may affect patient care.

Myocardial cannabinoid type 1 receptor imaging

Apart from the described detrimental effects of increased endocannabinoid plasma levels on the coronary circulatory function in obesity (21–24), they may also lead to an activation of myocardial cannabinoid type 1 receptors (CB1-R) that has been suggested as underlying cause for systolic heart failure via mitogen-activated protein kinases activation, angiotensin II receptor type 1 expression/signaling, advanced glycation end product accumulation, oxidative/nitrate stress, inflammation, and fibrosis (40). In this respect, we investigated the feasibility of targeted imaging of myocardial CB1-R and its potential up-regulation in obese mice with translation to humans using ^{11}C-OMAR and PET/CT imaging (41). And indeed, we could unravel a distinct increase in myocardial CB1-R uptake in obese as compared to lean mice, delineating myocardial CB1-R up-regulation in obese mice. Importantly, these in vivo findings by ^{11}C-OMAR and dynamic micro-PET/CT were validated with absolute quantification of myocardial CB1-R gene expression with droplet digital PCR and in situ hybridization and translated to humans (41). The observed up-regulation of myocardial CB1-R may indeed reflect a mechanistic link between obesity and the initiation and/or progression of obesity-related heart failure (20). If our hypothesis can be confirmed, then then new medical therapy strategies may evolve to target the blockage of myocardial CB1-R in obese and in particular in morbidly obese patients not undergoing gastric-bypass surgery. In addition, ^{11}C-OMAR and PET/CT imaging could evolve as unique imaging tool to gear and optimize medical treatment blocking myocardial CB1-R and thereby to individualize preventive medical care in obesity that, however, remains to be evaluated in the clinical setting.

Conclusions

Cardiac PET with assessment of myocardial perfusion and flow quantification with cardiovascular risk prediction in clinically-manifest and subclinical CAD has evolved as a mainstay in the clinical decision-making process. In this respect, cardiovascular PET continuous to expand its clinical scope with assessment of infiltrative-inflammatory cardiac disease, vasculitis, and device infections. Conversely, PET flow quantification for the identification and characterization of coronary circulatory dysfunction in conjunction with various biomarkers has provided unique "*in vivo*" insight into early functional stages of the CAD process that may complement or even guide experimental studies that investigate direct cause-effect relationships. Further, emerging radiotracer probes with PET may probe non-invasively myocardial receptor expressions, such as cannabinoid type 1 receptors that may play a role in heart failure development in obesity and / or diabetes mellitus deserving further clinical evaluation.

Acknowledgments

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Conflicts of interest

Consultant for Advanced Accelerator Applications International S.A.

Abbreviations and acronyms

CAD=coronary artery disease, CPT=cold pressor test, ^{18}F-FDG =^{18}F-fluoro-2-deoxy-glucose, MBF = myocardial blood flow, MFR=myocardial flow reserve, PET=positron emission tomography.

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