Molecular Imaging
Volume 17: 1-4

DOI: 10.1177/1536012117749052
journals.sagepub.com/home/mix
SAGE

Commentary to ^{18}F-GP1, a Novel PET Tracer Designed for High-Sensitivity, Low-Background Detection of Thrombi: Imaging Activated Platelets in Clots—Are We Getting There?

Andrew W. Stephens, MD, PhD[1], Norman Koglin, PhD[1], and Ludger M. Dinkelborg, PhD[1]

Abstract

Thrombus formation can lead to heart attacks, stroke and pulmonary embolism, which are major causes of mortality. Current standard diagnostic imaging methods detect anatomic abnormalities such as vascular flow impairment but have limitations. By using a targeted molecular imaging approach critical components of a pathology can be selectively visualized and exploited for an improved diagnosis and patient management. The GPIIb/IIIa receptor is abundantly and specifically exposed on activated platelets and is the key receptor in thrombus formation. This commentary describes the current status of GPIIb/IIIa-based PET imaging approaches with a focus on the recently published preclinical data of the small-molecule PET tracer ^{18}F-GP1. Areas of future research and potential clinical applications are discussed that may lead to an improved detection of critical thromboembolic events and an optimization of available antithrombotic therapies by tracking activated platelets.

Keywords

GPIIb/IIIa, 18F-GP1, platelets, embolism, thrombosis

Venous and arterial thromboembolism causing diseases like myocardial infarction, stroke, transient ischemic attacks, deep vein thrombosis (DVT), or pulmonary embolism are still a major cause of morbidity and mortality worldwide. Imaging plays a crucial role in the diagnosis of thrombotic events. Molecular imaging approaches combined with high-resolution anatomic imaging allow for tissue characterization on a molecular level to support a better diagnosis and potentially leading to improved therapeutic outcomes.

The current standard methods for thrombus imaging detect anatomic abnormalities, in this case vascular occlusions, and rely on different modalities depending on the vascular territory. Ultrasound is standard of care for DVT and carotid stenosis while computed tomography angiography (CTA) and spiral computed tomography are commonly used for detecting pulmonary emboli (PE) and peripheral arterial disease. Transesophageal ultrasound is required for atrial and valvular thrombi. A noninvasive whole-body imaging modality that can visualize thrombi from various sources in different anatomic regions together with information about an underlying pathological process would be very valuable. Current procedures elucidate space filling lesions but provide little information on the biological processes ongoing at the level of the occlusion and generally do not allow for reliable discrimination between fresh unstable (high risk) thrombi and chronic organized (stable) thrombi.

Thrombi expose numerous specific targets that can be examined by molecular imaging.[1] Among them are activated coagulation factors, the end product of the coagulation cascade, fibrin, as well as various epitopes on activated platelets. Fluorodeoxyglucose is the current workhorse in nuclear medicine departments; however, it plays only a limited or no role

[1] Piramal Imaging GmbH, Berlin, Germany

Submitted: 06/10/2017. Revised: 30/10/2017. Accepted: 07/11/2017.

Corresponding Author:
Andrew Stephens, Piramal Imaging GmbH, Tegeler Str. 6-7, 13353 Berlin, Germany.
Email: andrew.stephens@piramal.com

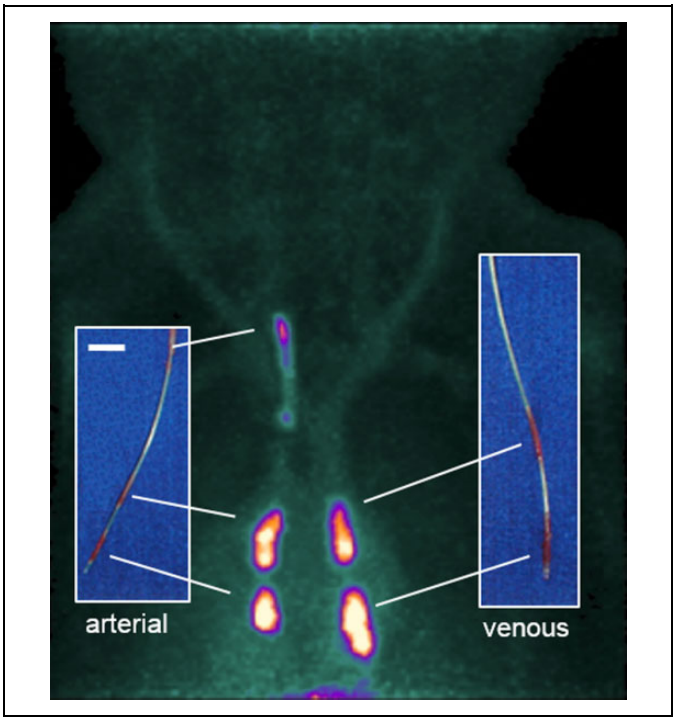

Figure 1. Positron emission tomography imaging of activated platelet deposition in a *cynomolgus* monkey model with a PET probe targeting GPIIb/IIIa receptors. Catheters with roughened surfaces at specific positions were introduced in the right carotid artery and into the vena cava. Both, the arterial and venous thrombi were detected after intravenous injection of 25 MBq of an ^{18}F-labeled elarofiban derivative. The image inserts show the catheters removed after the PET study. Only the roughened sites show thrombus formation that were also visualized by PET (white bar = 1 cm). PET indicates positron emission tomography.

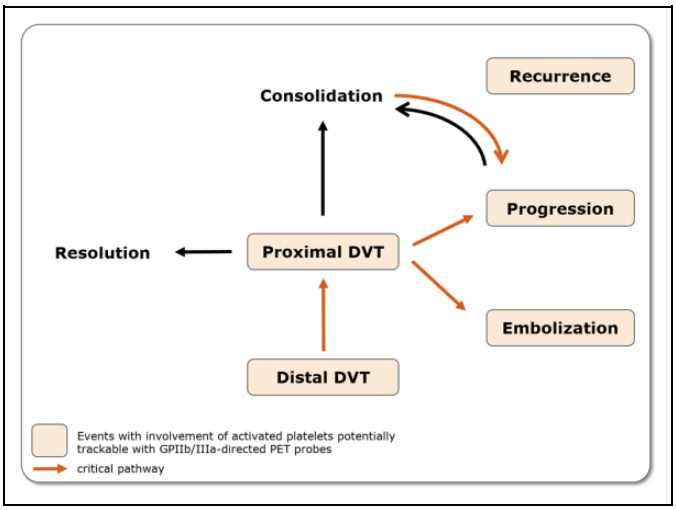

Figure 2. Proposed schematic representation of the development and fate of thromboembolic events with involvement of activated platelets at different stages. The ability to visualize and follow critical thromboembolic events using a GPIIb/IIIa-based PET imaging approach is highlighted. PET indicates positron emission tomography.

in thrombus detection and characterization. Fluorodeoxyglucose rather visualizes thrombus-associated inflammation, which can be considered as a surrogate marker of thrombosis, but is not linked to intrinsic pathological events in thrombus formation. In a growing thrombus, the key step of platelet aggregation is characterized by the binding of activated GPIIb/IIIa receptors to the arginine–glycine–aspartic acid (RGD) motifs on fibrinogen, which results in cross-linking. Imaging probes targeting either fibrin[2] or GPIIb/IIIa receptors currently appear the most promising.

The GPIIb/IIIa receptor, also known as $\alpha_{IIb}\beta_3$, is a member of the integrin family of cell surface proteins and is expressed specifically and in high density on platelets. It undergoes allosteric activation after stimulation of platelets by a variety of agents or vessel surface damages. The design and development of therapeutic IIb/IIIa inhibitors has attracted a considerable amount of interest in pharmacological research.[3] GPIIb/IIIa antagonists are commercially available, for example, abciximab (ReoPro; Eli Lilly Indianapolis, IN, USA), eptifibatide (Integrilin; GlaxoSmithKline), and tirofiban (Aggrastat, Cardiome Pharma Corp.). Tirofiban and eptifibatide are both small molecule synthetic RGD peptidomimetics.

Previous approaches to use GPIIb/IIIa receptors for targeted imaging failed because of a low affinity, lack of receptor specificity, poor blood clearance, or the low spatial resolution of the imaging technology used. Several previous imaging candidates, despite showing promising preclinical data, have not successfully been translated into clinical studies. Two new radiotracers, ^{18}F-GP1 and ^{64}CuMeCOSar, targeting the GPIIb/IIIa receptor have been described recently.[4,5]

^{18}F-GP1 is an elarofiban analog that can be efficiently ^{18}F-radiolabeled. The scaffold was selected based on its (1) very high specificity for binding GPIIb/IIIa over other closely related integrins,[6] (2) suitable pharmacokinetic properties,[7] and (3) feasibility for incorporating the ^{18}F-radiolabel without losing biological activity. In vitro analyses in human blood and explanted thrombi confirmed receptor binding.[4] As the binding of elarofiban and its derivatives to this receptor is species dependent, ^{18}F-GP1 was investigated in vitro in clots derived from human blood and in vivo in a nonhuman primate model (Figure 1). Small arterial, venous thrombi, thrombotic depositions on damaged endothelial surface, and small cerebral emboli were detected in vivo by positron emission tomography (PET) imaging. Clearance from the blood was nearly complete within 60 minutes.[4]

The ability for detecting clots and the favorable biodistribution in nonhuman primates supported the translation of ^{18}F-GP1 into the clinic. A phase 1 study is currently ongoing (NCT02864810). First results from an interim analysis were presented at the SNMMI 2017 annual meeting and confirm the preclinical data.[8] While the preclinical study and the first clinical trial were designed to obtain proof-of-concept and focus on clots of the large vessels, DVT, and pulmonary embolism, the ability to detect small thrombi with low vascular background may prove useful in various clinical applications. Many research questions remain, for example, the

size of the clot detectable, the age and composition of the clot, and whether an almost completely occlusive thrombus can be imaged. The other recently described GPIIb/IIIa radiotracer, ^{64}CuMeCOSar, a specific single-chain antibody against GPIIb/IIIa, has also shown promising preclinical characteristics.[5]

Provided that the first preclinical and clinical data are confirmed in bigger clinical studies, there are manifold potential uses of an activated platelet imaging agent. One of the most fundamental needs is to better understand the natural history of DVT, their progression to PE, and the real-time effect of therapeutic interventions. Small, often presymptomatic, lesions originate in calf vessels and migrate to the larger vessels in the thigh where they become symptomatic. These clots can resolve via endogenous fibrinolysis and monocyte/macrophages scavenging. They can consolidate with fibroblast ingrowth and eventual scar formation, damaging valves resulting in long-term sequelae, or they can progress locally or embolize to the lung. The ability to image simultaneously both space filling lesions and activated platelets longitudinally with PET/CT provides the opportunity to understand the conditions that favor one path over another in a unique manner (Figure 2). Sometimes a surprisingly large number of space-filling pulmonary lesions can be observed when evaluating PE with CTA. This has led to concern of an overdiagnosis of PE.[9,10] Not all of such PE lesions are the cause of symptoms. It will be very important to determine how long platelets remain activated in the embolic pathway and if patients with prolonged platelet activation are at higher risk of circulatory collapse, pulmonary hypertension, or the development of chronic occlusive pulmonary thromboemboli. Imaging activated platelets might be a tool to investigate the surface of implanted artificial devices such as catheters, heart valves, or stents. The potential to differentiate thrombotic from inflammatory processes would have a significant impact on therapeutic interventions such as the surgical replacement of such devices.

The ability to track activated platelets allows the optimization of antithrombotic therapies with the ability to titrate antithrombotic and antiplatelet agents. A potent armamentarium of anticoagulants is available for therapy, but these drugs can cause significant bleeding. There is a critical need to balance the risk of bleeding against the risk of clotting in each patient. Higher doses and combinations of antithrombotic and antiplatelet agents result in the occurrence of major bleeds, sometimes life-threatening. Individualizing therapy based on risk factors and real-time monitoring of the active process should allow for more effective and safer drug regimens. For example, high-risk patients who would benefit from the addition of antiplatelet agents can be identified. Therapeutic intensity and treatment duration remain issues that would benefit from these tracers.

Finally, tracking activated platelets is also an intriguing possibility for imaging atherosclerotic plaques. This is a long sought after application. Plaque imaging research has been ongoing for over 25 years. Improved sensitivity and spatial resolution of the latest PET cameras may allow detection of even small lesions. The ability to assess molecular processes ongoing within a lesion, to determine the extent of disease and to understand which lesions are vulnerable and at risk of rupture have proven to be a high hurdle. Given the high morbidity and mortality from plaque rupture, having an in vivo image of the vulnerable plaque and gaining more insight into platelet–plaque interactions are critical to improving therapies.

In conclusion, tracking activated platelets offers the unique ability to detect and characterize specific processes associated with thrombus formation and progression. More clinical research will elucidate which target and imaging probe will be best suited to address specific questions in assessing, risk-stratifying, and longitudinally tracking thromboembolic events to lower the burden of the disease.

Authors' Note

All authors are employees of Piramal Imaging GmbH, Berlin, Germany.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Wang X, Peter K. Molecular imaging of atherothrombotic diseases: seeing is believing. *Arterioscler Thromb Vasc Biol*. 2017; 37(6):1029–1040. doi:10.1161/ATVBAHA.116.306483.
2. Ay I, Blasi F, Rietz TA, et al. In vivo molecular imaging of thrombosis and thrombolysis using a fibrin-binding positron emission tomographic probe. *Circ Cardiovasc Imaging*. 2014; 7(4):697–705. doi:10.1161/CIRCIMAGING.113.001806.
3. Hanson J, de Leval X, David JL, Supuran C, Pirotte B, Dogné JM. Progress in the field of GPIIb/IIIa antagonists. *Curr Med Chem Cardiovasc Hematoll Agents*. 2004;2(2):157–167.
4. Lohrke J, Siebeneicher H, Berger M, et al. 18F-GP1, a novel PET tracer designed for high-sensitivity, low-background detection of thrombi. *J Nucl Med*. 2017;58:1094–1099. doi:10.2967/jnumed.116.188896.
5. Ziegler M, Alt K, Paterson BM, et al. Highly sensitive detection of minimal cardiac ischemia using positron emission tomography imaging of activated platelets. *Sci Rep*. 2016;6:38161. doi:10.1038/srep38161.
6. Hoekstra WJ, Maryanoff BE, Damiano BP, et al. Potent, orally active GPIIb/IIIa antagonists containing a nipecotic acid subunit. Structure-activity studies leading to the discovery of RWJ-53308. *J Med Chem*. 1999;42(25):5254–5265.

7. Damiano BP, Mitchell JA, Giardino E, et al. Antiplatelet and antithrombotic activity of RWJ-53308, a novel orally active glycoprotein IIb/IIIa antagonist. *Thromb Res*. 2001;104(2):113–126.
8. Jin S, Lee JS, Han Y, et al. Exploratory clinical trial of [18F]GP1 for imaging arterial or venous thromboembolism using positron emission tomography: interim analysis of an open-label, single center study. *J Nucl Med*. 2017;58:438.
9. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med*. 2011;171(9):831–837. doi:10.1001/archinternmed.2011.178.
10. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. *BMJ*. 2013;347:f3368. doi:10.1136/bmj.f3368.