Scintica:

A Non-Invasive Method to Assess Coronary Flow Reserve

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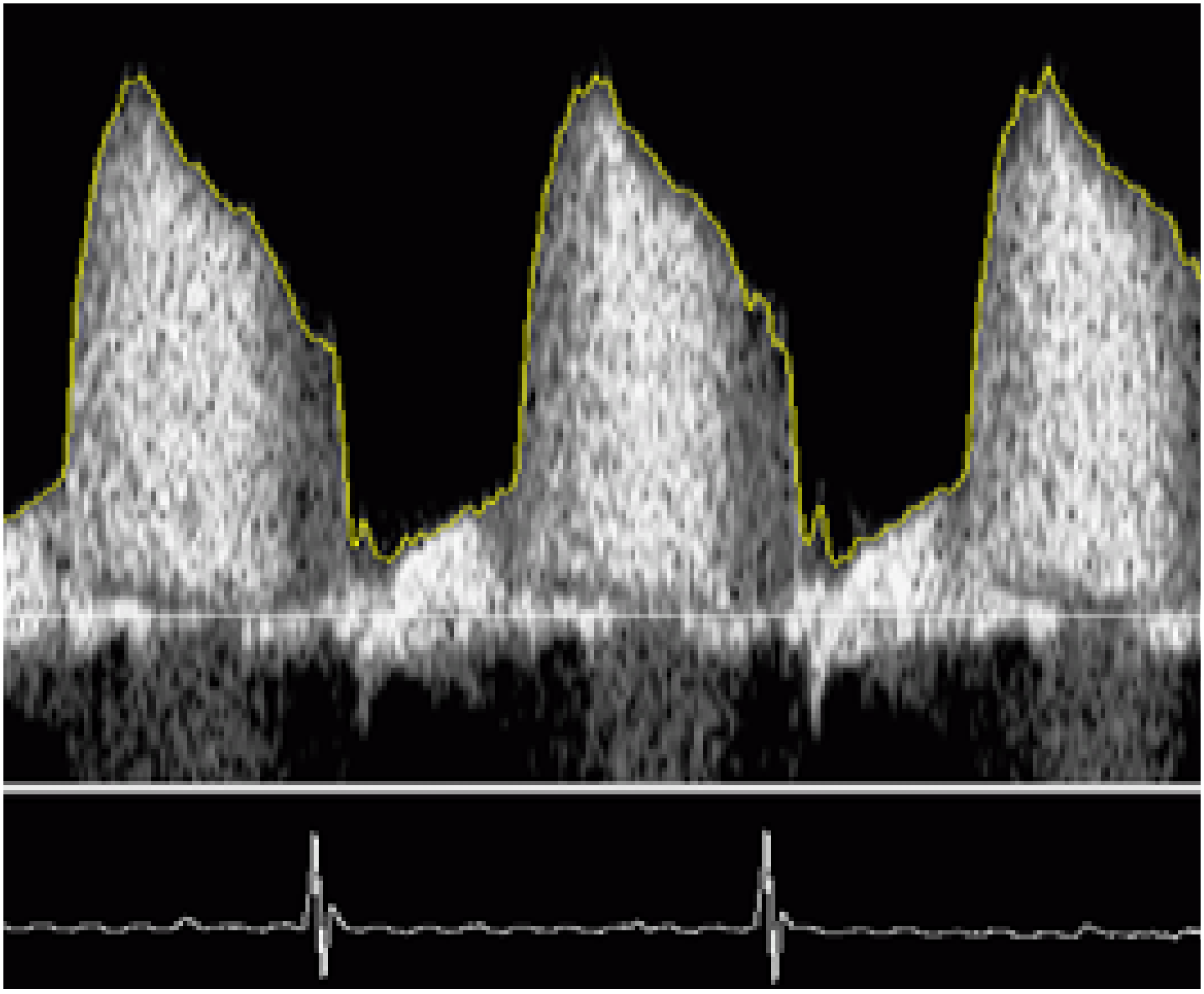

Coronary flow reserve (CFR) is the term used to describe the maximum increase in blood flow through the coronary arteries above the normal resting volume. CFR is reduced by age, as well as various disease states including coronary artery disease. Given the small size and significant branching of these arteries, traditional methods for assessing coronary flow are highly technical and invasive, such as invasive flow probes and coronary catheters. Echocardiography or ultrasound imaging may also be employed, however, can be quite costly.

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Isoflurane is a commonly used anesthetic agent and is also a potent vasodilator. When coupled with a non-invasive Doppler flow velocity technology, it can be used to assess CFR in rodent models. Hartley and colleagues provide an excellent example of this by comparing CFR in young C57BL6 wild-type, old ApoE+/+ wild-type, and old ApoE-/- knockout mice using the Doppler flow velocity system manufactured by Indus Instruments1. Animals were anesthetized and a 2 mm diameter, 20 MHz Doppler probe was placed on the left side of the chest at the level of the cardiac base. It was pointed horizontally towards the basal surface of the heart to identify coronary flow signals on the Doppler spectral display. Once identified, the probe was fixed in place using a micromanipulator, resulting in a sound beam near parallel to the axis of the left main coronary artery. Unlike echocardiography probes, the Doppler probes can be oriented at a very acute angle relative to the direction of blood flow resulting in less error and no need for angle-correction. (To learn more about measurement error related to probe angle, see the following document).

To assess CFR, isoflurane was increased to 2.5% and then reduced to 1% to get a ratio of hyperemic to baseline coronary flow (H/B). A baseline measure was collected at 1%. The ratio was significantly different between old mice and young mice and between ApoE-/- mice and age-matched controls. These findings provide evidence that Doppler is an effective, non-invasive technique for assessing CFR in vivo. The authors also highlight the importance of considering the anesthetic agent and dose when assessing coronary flow in mice, given its potent and rapid effect on vasodilation.

In another study, Chintalgattu and colleagues used Doppler to examine the mechanism of cardiotoxicity of anticancer platelet-derived growth factor receptor (PDGFR) inhibitors2. Platelet-derived growth factor (PDGF) isoforms exert their proangiogenic effects through interaction with class III receptor tyrosine kinases, PDGFRα and PDGFRβ. Binding induces angiogenesis, in part via upregulation of vascular endothelial growth factor (VEGF) production.These receptors are also expressed on malignancies and are targeted by receptor tyrosine kinase (RTK) inhibitors including sunitinib, sorafenib, and imatinib. Unfortunately, myocardial dysfunction and heart failure have been reported among patients treated with these agents. In this study, researchers sought to examine the role of PDGFR signaling in the heart to provide further insight into the mechanism of cardiotoxicity of anticancer PDGFR inhibitors. They hypothesized that PDGFR signaling may play a role in the cardiac response to vascular stress such as hypertension.

To test this hypothesis, C57BL/6 mice, cardiac-specific PDGFR-β-knockout mice (PdgfrbNkx-Cre), mice with PDGFR-β flanked by loxP sites (controls, Pdgfrbfl/fl) and inducible, cardiac-specific PDGFR-β-knockout mice (PdgfrbMerCre) were used.

Transaortic constriction (TAC) was applied to induce heart failure. In addition to Doppler flow velocity, echocardiography, magnetic resonance imaging, RT-PCR, gene expression microarrays and cell culture assays were performed to assess CFR. Blood flow velocity in the coronary arteries was measured at 24 hours, 7 days and 14 days following TAC using the Indus

Hyperemic coronary flow in PdgfrbMerCre mice was reduced at baseline and following pressure overload (TAC). The minute augmentation in response to the isoflurane vasodilatory stimulus indicated impaired coronary microvasculature in this group. Taken together, these results suggest a potential mechanism by which anticancer PDGFR inhibiting agents may contribute to cardiotoxicity. Specifically, the response to load-induced stress is mediated, in part, by PDGFR-β signaling stimulating angiogenesis.

These two studies demonstrate the simplicity of non-invasive Doppler blood flow determination of coronary flow reserve. Chintalgattu et al. provide insight into the effects of anticancer agents on the coronary microvasculature however, there are a myriad of other disease states and therapies that can be assessed using CFR. Non-invasive assessment of coronary flow velocity with the Doppler flow velocity system is an excellent alternative to invasive flow probe and catheter procedures and provides accurate and reproducible results for in vivo animal studies.

Cited References:

1. Hartley, C. J. et al. Effects of Isoflurane on Coronary Blood Flow Velocity in Young, Old and ApoE-/- Mice Measured by Doppler Ultrasound. Ultrasound Med. Biol. 33, 512–521 (2007).
2. Chintalgattu, V. et al. Cardiomyocyte PDGFR-beta signaling is an essential component of the mouse cardiac response to load-induced stress. J. Clin. Invest. 120, 472–84 (2010).