

## Dissecting myocardial signal transduction cascades: Sharp new insights from multi-tracer molecular imaging

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The potential to combine tracers for interrogation of several components of disease within a single imaging session has always been a strength of nuclear imaging. In conventional scintigraphy and SPECT, this can be achieved by sequential or simultaneous imaging of two isotopes with different photon energies. Examples are the combination of thallium-201 and Tc-99m-labeled agents for rapid assessment of myocardial perfusion at rest and stress,<sup>1,2</sup> or the combination of iodine-123- or indium-111-labeled molecular-targeted tracers with a perfusion imaging agent.<sup>3,4</sup> In PET, this is achieved by sequential imaging of two or more short-lived compounds. Examples are the combined assessment of myocardial perfusion and glucose utilization for determination of myocardial viability,<sup>5</sup> or the combination of multiple radiolabeled substrates for detailed investigation of cardiac metabolism.<sup>6</sup>

The advent of molecular imaging results in an increasing variety of increasingly specific tracers.<sup>7,8</sup> When used alone, these tracers provide a snapshot of the presence or absence of abnormality of the interrogated molecular target structure. This snapshot may be difficult to interpret, because the role of upstream or downstream events along the signal transduction cascade remains obscure. Combination of multiple tracers, which target a series of different molecules along a signal transduction cascade, would thus be attractive. Dissection of the cascade would not only allow for

improved understanding of pathogenetic mechanisms, it may also allow for identification of the most relevant molecular target structure, which is most severely affected by the disease. This structure may then serve as a single target in subsequent efforts to simplify imaging for broader clinical application.

The study by Kenk et al in this issue of the *Journal of Nuclear Cardiology* is an elegant and innovative step into this direction.<sup>9</sup> The authors chose the sympathetic nervous system, which is of increasing interest to the cardiovascular imaging community due to its key role in regulation of contractility and electromechanic properties in health and disease.<sup>10-12</sup> They combined three different tracers to dissect noradrenergic signaling in a rodent model of anthracycline-induced cardiotoxicity. For this purpose, they did not only use a radiolabeled catecholamine analogue to look at presynaptic nerve terminal integrity and a radiolabeled beta-adrenergic receptor ligand to look at postsynaptic receptor density—an approach that had been pursued by others before.<sup>13-15</sup> Importantly, the authors added a marker of downstream signaling to their mix, namely the phosphodiesterase inhibitor carbon-11 rolipram which is involved in regulation of cyclic AMP. In brief, the authors found no significant change in presynaptic catecholamine uptake and downstream phosphodiesterase binding, but they observed a significant reduction in postsynaptic beta-receptor density after 3 weeks of treatment with anthracycline, at a time where cardiac function was still preserved. On the one hand, their results suggest that, if a single tracer is sought for early clinical detection of cardiotoxicity, beta-adrenergic receptor imaging may be the best choice. On the other hand, the observation that upstream presynaptic catecholamine uptake as well as downstream cyclic AMP regulation can remain unchanged despite changes in receptor density as the intermediary structure in the signaling cascade is new and needs to be clarified in further mechanistic studies.

Some limitations of the work by Kenk et al need to be recognized. Firstly, the study was done using autoradiography, not in vivo imaging. Autoradiography allows for a robust, high-resolution assessment of myocardial radioactivity, but it is a post-mortem ex vivo

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technique and eliminates factors such as bloodpool activity, partial volume effects, and metabolites which are critical to the feasibility of in vivo imaging. Secondly, myocardial blood flow was not determined. Myocardial retention of the employed tracers may be flow-dependent, and differences in flow-dependency of those tracers may explain differences in their ability to detect cardiotoxicity. And finally, the rat was used as a model but the sympathetic nervous system in these small rodents may differ from that in larger mammals and humans.<sup>16</sup> More work will be necessary to determine the feasibility and robustness of this multi-tracer approach for in vivo imaging and to translate it into a clinical setting.

Despite these limitations, the study by Kenk et al should still be seen as highly innovative and stimulating work, which represents an important early step into the right direction: In times of an ever increasing specificity of molecular medicine, the combination of multiple probes will provide deeper insights into molecular pathways and will help to further establish the value of noninvasive targeted imaging. It is with this work like with most innovative projects: Further questions arise, and a stimulus for subsequent efforts is provided. Based on the results of this study, it is likely that we will see additional investigations into the pathobiology of noradrenergic signaling, further efforts to establish in vivo imaging methodology, and further work to translate the knowledge into a clinical setting in the future.

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