testing might be very fallacious when the issue is prognosis. For instance, in coronary artery disease, highly sensitive tests that work finely even in the identification of minor vessel disease do not have a prognostic counterpart as minor forms of coronary artery disease are not life-threatening. In the field of stress echocardiography, this problem has been clearly demonstrated when, in order to increase test sensitivity, both for dobutamine and dipyridamole atropine was added. Sensitivity increased but the subset of patients with test positivity after atropine did not have any difference in survival when compared with the subset with a negative test. We could have employed a more aggressive ‘diagnostic’ approach also in this set of patients by using cut-off values higher than 2.5, but prognostic testing needs a more conservative approach. In the ‘fisherman’s approach’, proposed by Ostojic from Belgrade, we need a net with big holes to catch the bigger fish of disease giving prognostic troubles. The holes will be smaller with aggressive testing giving optimal diagnostic values. What works efficiently in diagnostic testing could be translated into a poor prognostic test at least in the short-medium run. In our patient population, 14 patients had a CFR >2.5 and they had a 80% survival rate. We agree that CFR, in this set of patients, cannot be considered the sole parameter to be evaluated but is one among others able to risk stratify patients identifying those needing a more aggressive approach due to the severity of the disease. As reported in the univariate and multivariable analyses, several parameters were able to identify patients at risk of experiencing spontaneous events. The multivariable analysis reported in the results section of the manuscript identified severity of mitral insufficiency, abnormal CFR, and resting WMSI as independent predictors of survival. In the conclusions of the manuscript, there was no intention of implying that more conventional clinical and echo parameters in the evaluation of patients with non-ischaemic dilated cardiomyopathy should be discarded. The routine use of CFR assessment allowed us to obtain interesting pathophysiological information that have a practical impact, transferable into the clinical arena, at reasonable costs and minimizing acute and long-term risks. We fully agree with Dr De Gregorio that CFR is a complementary parameter easily obtained during vasodilatory stress echo along with ejection fraction, volumes, mitral regurgitation, and regional function both at rest and at peak stress. The worst mistake that a clinical cardiologist can make is to view these novel parameters entering the prognostic scenario in an agonistic-competitive view with old, time-honoured parameters of established usefulness. We thank Dr De Gregorio for reminding us this obvious but frequently forgotten fact. Altogether, these parameters provide a powerful means of stratification just in one sitting during a single exam.

References
6. Agricola E, Oppizzi M, Pisani M, Margonato A. Prognostic testing needs a more conservative approach also in this set of patients by using cut-off values higher than 2.5, but prognostic testing needs a more conservative approach.5 In the ‘fisherman’s approach’, proposed by Ostojic from Belgrade, we need a net with big holes to catch the bigger fish of disease giving prognostic troubles. 3 The worst mistake that a clinical cardiologist can make is to view these novel parameters entering the prognostic scenario in an agonistic-competitive view with old, time-honoured parameters of established usefulness. We thank Dr De Gregorio for reminding us this obvious but frequently forgotten fact. Altogether, these parameters provide a powerful means of stratification just in one sitting during a single exam.

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Iloprost attenuates doxorubicin-induced cardiac injury in a murine model without compromising tumor suppression

The article by Neilan et al.1 [May 27(10) issue of this journal] is of interest to us. Their group has documented that iloprost attenuates the doxorubicin (DOX)-induced cardiac cell death in vitro and in vivo.2,3 They extend the work and estimate the effect of iloprost on DOX-induced cardiac dysfunction and anti-cancer therapy. Their message is clear, but this study raises some questions.

The authors mention that cardiac sections from animals treated with iloprost + DOX show none of the pathological changes seen in the DOX group and are indistinguishable from controls. Certainly, iloprost attenuates DOX-triggered cardiac cell death and dysfunction. However, there are around 4–5% of cardiomyocyte loss even in iloprost + DOX group with a small increase of TUNEL-positive cells (cf. about 10% of cell reduction in DOX group; Figure 3). Why did the authors fail to detect such a huge change in histological analysis? Moreover, the degradation of titin, a critical sarcomere player in the regulation of contractile function, is an early event in DOX-induced cardiac injury and consequent necrosis.4 In this animal model, comparatively high dose of DOX was used in short duration, and it might induce cardiomyocyte necrosis rather than apoptosis.5 Therefore, myofibrillar disarray may be a better parameter than cardiac fibrosis to estimate acute DOX toxicity.

Despite problems as mentioned earlier, their work is interesting since it has a potential that directly links to the strategy to prevent anthracycline cardiotoxicity. One of their next goals is the mechanism of this prostacyclin protection against DOX-induced cardiac injury. Cicaprost, another prostacycline analogue, which activates IP and EP but not PPAR, may indicate a beneficial information. We are looking forward to their next challenge.

References
2. Adderley SR, Fitzgerald DJ. Oxidative damage of cardiomyocytes is limited by extracellular regulated kinase 1/2-mediated induction of
Iloprost attenuates doxorubicin-induced cardiac injury in a murine model without compromising tumor suppression: reply

We would like to thank Drs Kuramochi, Takagi, and Morita for their interest in our work. Although measurement of apoptosis using the TUNEL assay is validated and extensively published in this model,\textsuperscript{1,2} we agree that, likely due to the transient nature of the process, a significant proportion of apoptotic nuclei will not be detected and, either due to sample harvesting, preparation, and staining protocols, a percentage of false positive results will be reported. The second point raised is also of considerable interest, as, although TUNEL-positive cells have been detected as early as 24 h after administration of doxorubicin in animal models,\textsuperscript{3} discordance has been suggested in the extent of the ventricular dysfunction and the degree of apoptosis. This discordance may be explained by the effect of doxorubicin on large myofilament proteins such as titin.\textsuperscript{4} Finally, we agree that further work, such as that suggested, is required to differentiate whether the protective effects of iloprost are mediated via prostacyclin or nuclear hormone receptors.

References


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