EDITORIAL

Neuronal damage and abnormal contraction: Is the circle of synchronicity complete?

Claudio Marcassa, MD[a]

[a] Cardiology Department, Maugeri Clinical and Scientific Institutes, IRCCS, Scientific Institute of Veruno, Veruno, NO, Italy

Received Dec 5, 2017; accepted Dec 6, 2017
doi:10.1007/s12350-017-1167-6

See related article, pp. 869–879

Asynchronous cardiac contraction is considered one of the substrates of heart failure. Myocardial ischemia, fibrosis, or conduction disturbances are the pieces of a complex puzzle that lead to a regional delayed contraction and ultimately to an asynchronous intraventricular contraction. Since early '80s, it is known that the amount of asynchrony is significantly and inversely correlated to the global left ventricular (LV) systolic function.[1]

Several imaging techniques are currently available to evaluate and quantify the presence of inter- and intraventricular asynchronous contraction. Echocardiography (M-mode, 2D, Tissue Doppler Imaging, strain, strain rate, tissue tracking, and three-dimensional imaging) is an imaging modality widely available to cardiologists for the assessment of asynchrony. However, most of the proposed methods are limited by the use of a single imaging plane and the operator dependency, which affects the reproducibility of the measurements obtained, particularly those related to the intraventricular asynchrony. In addition, it is still unclear which parameters may actually allow the accurate identification of responders to resynchronization therapy.[2]

Concerning the correlation between surface 12-lead ECG and mechanical asynchrony, it was documented by radionuclide ventriculography that intra- and interventricular asynchrony are well correlated with the amount of QRS widening or the LV ejection fraction value.[3]

At the end of the last millennium, it was observed that a decrease of sympathetic tone to the heart resulted in an asynchronous wall motion pattern and an impaired LV relaxation;[4] a close correlation between LV dyssynchrony and impaired myocardial sympathetic tone has been then hypothesized. In a group of 83 patients undergoing an evaluation of LV perfusion and sympathetic innervation on ^{99m}Tc-tetrofosmin/^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) imaging, it was documented that patients with LV dyssynchrony showed an elevated burden of ''innervation/perfusion'' mismatch that is concentrated at the level of the most dyssynchronous walls.[5] Moreover, the extent of regional innervation/perfusion mismatch was also an independent predictor of LV diastolic abnormalities.[6]

On the other side, in patients with dual-chamber pacemaker it was observed that stimulation from the apex of the right ventricle is responsible for regional alteration of the adrenergic innervation of the left ventricular myocardium, as assessed by I(123)-MIBG activity.[7]

Magnetic resonance imaging (MRI) has also been used to assess ventricular asynchrony and its response to pacing therapy.[8,9] In patients with non-ischemic heart failure, spatial dyssynchrony, as assessed by cross-correlation analysis of time curves of myocardial circumferential strains delivered from cine-tagging MRI images, was correlated with an impairment of cardiac sympathetic activity.[10] MRI, however, is affected by limited availability, the technique is time consuming, and several patients cannot be studied (i.e., those with ICD-CRT devices, in particular before and after implantation).

In this issue of the Journal, Cruz et al., in a group of 81 patients with heart failure and reduced LV ejection fraction submitted to cardiac resynchronization therapy

Reprint requests: Claudio Marcassa, MD, Cardiology Department, Maugeri Clinical and Scientific Institutes, IRCCS, Scientific Institute of Veruno, Via Per Revislate 13, 28010, Veruno, NO, Italy; *claudio.marcassa@icsmaugeri.it*

J Nucl Cardiol 2019;26:880–2.
1071-3581/$34.00

(CRT), tested the hypothesis that regional myocardial contractility is linked to the integrity of local autonomic innervation; this would allow an indirect estimation of cardiac autonomic dysfunction.[11] They used the longitudinal strain as determined by speckle tracking in 2D echocardiography as a surrogate for cardiac autonomic dysfunction. Cruz et al. documented a statistically significant correlation between strain and heart/mediastinum ratio with MIBG both at baseline and 6 months after CRT. Echocardiography, obviously, is the imaging modality cardiologists are more confident with, and is easily available. However, the best method and index for the assessment of LV asynchrony with echocardiography is still to be defined. Nuclear cardiology techniques, however, offer the possibility to quantify LV asynchrony from gated SPECT perfusion or blood pool images by phase analysis software in an almost automatic and highly reproducible way. Moreover, with myocardial perfusion gated SPECT images an integration of perfusion, function, and asynchrony is obtained in a single study. Nevertheless, in this manuscript Cruz et al. reversed the point of view, estimating the neuronal damage from a more sophisticated regional contraction analysis with speckle tracking echocardiography.

Left ventricular mechanical dyssynchrony and impairment of cardiac sympathetic innervation are synergistically related to lethal cardiac events, contributing to better stratification of lethal cardiac event risks and probably to the optimization of therapeutic strategy.[12] Different results were obtained by Manrique et al., who observed that, in 94 patients with non-ischemic DCM undergoing I-123 MIBG imaging for assessing cardiac sympathetic innervation and equilibrium radionuclide angiography to assess LV asynchrony by phase analysis, I-123 MIBG uptake, but not intra-LV asynchrony, was predictive of clinical outcome.[13] Furthermore, in a subgroup of ADMIRE-HF patients undergoing rest gated SPECT Tc-99m and I-123 MIBG imaging, LV mechanical dyssynchrony, as assessed by phase analysis of SPECT perfusion images, was independently associated with potential lethal arrhythmic events.[14]

Asynchronous LV contraction is the final result of a complex interaction among viability, innervation, and electrical derangement (Figure 1) and affects global LV function and patients' prognosis;[15] while viability and dyssynchrony can be evaluated by different imaging modalities (i.e., nuclear, echo, and MRI), innervation can only be assessed by nuclear techniques. Each of the three factors, taken singularly, was correlated to patients' prognosis,[16-18] as well as the combination of denervation and viability (mismatch extension).[19] However, the relative contribution of the three factors involved in the asynchrony to patients' prognosis and, in particular, to the type of hard events (i.e., lethal arrhythmias or worsening heart failure, information useful to plan patients' management), or their accuracy in identifying those patients prone to improve after resynchronization therapy, requires additional studies.

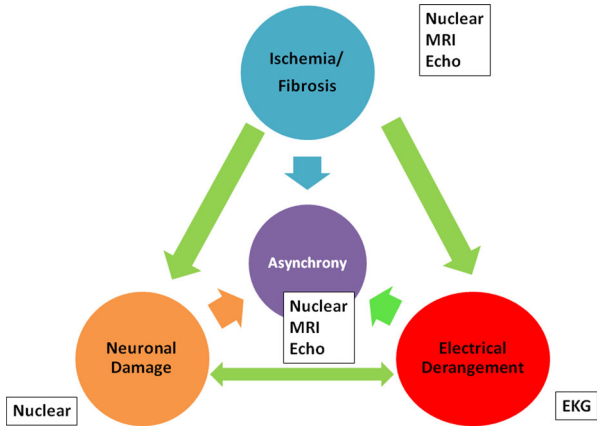

Figure 1. Relation of ischemia/fibrosis, neuronal damage, and electrical derangement between each other and with ventricular asynchrony. *MRI* magnetic resonance imaging.

Disclosure

None.

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