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EDITORIAL

Assessment of Longitudinal Myocardial Stiffness Is Not Enough to Evaluate Diastolic Function

– What Is the Relevance of the Stiffness of Cardiomyocytes in the Transverse Direction? –

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From the pioneering works of Otto Frank and Ernest H. Starling by the end of the 19th century and in the early 20th, myocardial function began to be the subject of intensive studies. However, the numerous studies published at the time only referred to myocardial contraction and not to the diastolic component. This overlooking of the diastolic component was possibly because ventricular filling was considered a completely passive process that occurred only as a result of pressure gradients. In the 1960s, the first studies of diastolic function appeared and from there the interest in this phase of the cardiac cycle increased. Such interest has continued to the present day, when systole and diastole are equally considered. It should be added that in the past 2 decades the prevalence of heart failure with preserved ejection fraction has increased, and the prognosis of those patients with diastolic dysfunction is poor.[1] Detailed study of the diastolic function, not only in intact animals or in patients, but in isolated organs as well, and even at the cellular level, has enabled clear differentiation of 2 phases in the diastolic component: isovolumic relaxation, and myocardial stiffness.

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For several years these 2 phases were independently studied, but it was later observed that interaction between them does exist, and that it can modify not only ventricular filling, but ventricular contraction as well.[2] More specifically, it was found that incomplete relaxation can be completed during ventricular filling, increasing myocardial stiffness.

This concept explained the increase in myocardial stiffness in different heart diseases.[3] Similarly, for a long time, the concept stating that changes in myocardial stiffness required a prolonged time frame and that included mainly extracellular matrix remodeling persisted. However, at present it is known that myocardial stiffness can be acutely modified within a few minutes by changes in the phosphorylation of myocyte proteins – sarcomeric as titin – or from the cytoskeleton, such as microtubules and intermediate filaments.

Recent studies have shown that it is possible to assess myocardial stiffness, not only of the ventricle as a whole, but in isolated myocytes as well, which has extended knowledge of both the cellular and molecular mechanisms that regulate myocardial stiffness. Thus, it has been possible to relate the incomplete relaxation phenomenon with an increase in myocardial stiffness, now under more strict control of the variables. However, all of those studies have considered longitudinal myocyte changes, and did not assess modifications that could occur in the transverse axis. Consideration of changes in the longitudinal and transverse axes of the myocytes is particularly important when we address the fact that the structure of the ventricular wall and its cellular distribution is based on helicoidal muscular beams that intercross, giving the ventricular wall the appearance of a grid, which implies that if we would perform a transverse cut to the left ventricle, we would observe in that same cut some myocytes in the longitudinal axis, and others in the transverse axis. That complex structure of the ventricular wall indicates that resistance to stretching, which occurs during each cardiac cycle, is not going to be the same when we observe the myocyte either longitudinally or transversely. Hence, mechanical stress is not only transmitted longitudinally but transversely as well. In other words, during the cardiac cycle, while some myocytes would be generating a given stiffness along the longitudinal axis, others are going to be generating it along the transverse axis. Consequently, the influence on stiffness of incomplete relaxation will not be the same either.

In regard to this, Yoshikawa et al[4] assessed the effect of incomplete relaxation on myocyte stiffness along the transverse axis, in a model of myocardial hypertrophy induced by chronic administration of isoproterenol. The authors conclude that an alteration in the formation of the actin and myosin cross-bridges, which induced a state of incomplete relaxation, determined the increase in the myocytes' transverse stiffness. The administration of butanedione monoxime, an inhibitor of the actin-myosin interaction, reversed the stiffness increase, thus confirming the described phenomenon. Although the concept of transverse stiffness of myocytes has been described previously,[5] in the study by Yoshikawa et al,[4] this phenome-

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non of transverse stiffness as associated with incomplete relaxation is mentioned for the first time with clear experimental evidence.

The importance of this finding is major for Cardiology because it shows that myocardial stiffness can be modified, not only longitudinally, but transversely as well. If we review the previous paragraphs with regard to the helicoidal structure of the ventricular wall, maybe we can better understand the importance of assessing stiffness along both axes for a more integral knowledge of myocyte behavior in terms of stiffness during the cardiac cycle.

From this new description of transverse stiffness and its relation to incomplete relaxation, it could be concluded that evaluation of the relation isovolumic relaxation-stiffness that has been carried out so far has been partial, in so far as it only considered the longitudinal axis of the myocyte. Evaluation of this diastolic variable by considering now both axes would certainly modify at least some of the results obtained in previous studies that only considered the longitudinal axis. Also, it is interesting to observe that transverse stiffness, assessed in skeletal muscle cells, shows regional differences in the same myocyte; for example, the transverse stiffness that Z-disks support is different from that at the level of the M-line in the sarcomeres and this difference in the resistance of the transverse axis could modify intracellular signals induced by proteins structurally extra-sarcomeric perpendicular to the long axis in the muscular fiber.[6] The mechanical properties of the M-band, which is affected by transverse stiffness, are also important; for example, the titin kinase domain, which performs as mechano-receptor, is located at the M-band[7] and consequently, it can be assumed that lateral mechanical elements of the extra-sarcomeric cytoskeleton, which connect the myofibrils laterally, are important for maintaining the uniform length of the sarcomeres during activation.

Remembering that the uniform length of the sarcomeres is necessary to obtain maximum strength, we can conclude that the systolic properties of the muscle fiber are related to the lateral mechanical properties.

Although it becomes clear that the stiffness of a stretched muscle increases with the number of actin-myosin cross-bridges, it is less well known whether this bridge intercrossing is sufficient to modify myocardial stiffness at the beginning of diastole. Even though it has been described that there are bridges intercrossing throughout the whole cardiac cycle, it is not known whether this would suffice to increase the passive elastic component during diastole. Should this be the case, it could have a deep impact on ventricular function and could be the target of therapeutic actions. Hence, the study by Yoshikawa et al in the current issue of the Journal is important because it shows that passive myocardial stiffness in the transverse direction is increased in hypertrophic hearts with diastolic dysfunction. Also, the authors show that this increase in transverse myocardial stiffness is caused by the formation or existence of residual bridges in actin and myosin filaments, which could be prevented by administering an inhibitor.

It is still unclear which percentage of transverse and longitudinal stiffness contributes to total myocardial stiffness, although there is no doubt that both are important in regulating the diastolic function of the myocyte, and this is even more relevant in the context of pathologies such as hypertrophy or heart failure.

It could be speculated that an extensive evaluation of the myocyte, which would consider its 2 axes, could explain otherwise contradictory results in the different published studies, or maybe it could be said that when considering only one of the myocyte's axes, the results on myocardial stiffness could be underestimated, particularly in studies on hypertrophy where myocardial structure is obviously more complex than in the normal heart and therefore, by having a different distribution of intramyocardial forces, the stiffness of the longitudinal and transverse axes could also be modified.

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