Review of: "Disorganization of intercalated discs in dilated cardiomyopathy"

Mohamed Chahine[1]

1 Université Laval

Potential competing interests: The author(s) declared that no potential competing interests exist.

Dilated cardiomyopathy (DCM) is the most common cause of heart failure (HF). It induces the dilatation of cardiac cavities and impairs contractility and systolic function. It accounts for over 90% of all cardiomyopathy cases referred to specialized centers and is collectively the most common reason for heart transplants in the young. In this paper by Ito et al., (DOI: 10.1038/s41598-021-90502-1), the authors investigated morphological differences in intercalated discs (ICDs) from patients who died from DCM by comparing them to control hearts and hearts obtained from patients with congestive heart failure (CHF). The authors have previously observed morphological changes to ICDs due to volume overload and compensatory heart enlargement using a rabbit AV shunt model (DOI: 10.2353/ajpath.2010.090348). They suggested that ICDs exhibit waving dynamics for sarcomere assembly and disposal to adapt volume load changes in proportion to cardiac dilatation and myocyte elongation. N-cadherin is predominantly expressed in the heart and is localized in ICDs. This adherent protein plays an important role in maintaining the structural integrity of cardiomyocytes by anchoring ICDs to the cytoskeleton in myocytes. N-cadherin knockout is associated with DCM. The sequential contraction of the cardiac chambers depends on the orderly spread of excitation from one cardiomyocyte to another through ICDs. In this paper, the authors hypothesized that the intensity of N-cadherin immunostaining of ICDs may be reduced.

To test this hypothesis, the authors selected twenty-one autopsy cases from the archives of the Department of Pathology at Akita University in Japan. They were classified as eight control hearts, nine hearts from patients who died from CHF, and five hearts from patients who suffered from DCM based on their clinical diagnosis. The patients were younger in the DCM group, with an average age of 50.5 years. The average age of the control and CHF groups was 65.0. Most hearts were from males. As expected, the average heart weights were higher in the CHF and DCM patients than in the control patients. The average ejection fraction (EF) was significantly lower ($P<0.05$) in the patients with DCM. However, no correlation between heart weight and EF was observed in the control and CHF groups.

Macroscopic findings of autopsy hearts showed, in the DCM group, that the lumen of the LV was dilated and that the wall was thin, with an average thickness of 7.2 mm compared to 14.1 mm and 12.3 mm for the control and CHF groups, respectively. The DCM hearts were also characterized by irregular fibrosis and a higher left ventricular (LV) volume than the control group. The lumen of the LV was dilated and thinner in the CHF group than in the control group with, however, a great deal of variation.

The authors also compared the histology of the groups of hearts, including assessments of cardiomyocyte hypertrophy, cardiomyocyte elongation, nuclear pleomorphism, interstitial fibrosis, and myofibrillar loss. Overall, the authors found that the cardiomyocytes were thinner in the DCM group than in the control group, with the presence of fibrosis between the myocytes. The ICDs in the DCM were not clearly visible compared to the control and CHF groups. However, the differences in histological findings between the control and CHF groups were not significant. In addition, no significant difference in cardiomyocyte length was observed among the three groups.

The immunohistochemical findings with respect to N-cadherin revealed significant differences, with a disorganization of the ICDs in the DCM group compared to the control and CHF groups.

The transmission electron microscopy (TEM) findings confirmed that the DCM group exhibited ICD ultrastructure disorganization and sarcomere derangements compared with the control and CHF groups. Further pathological measurements revealed that the DCM group exhibited an increase in cardiomyocyte length, an increase in ICD scattering, and an increase in ICD widths. Surprisingly, a gene expression analysis of several genes associated with the ICD, including CDH2, the gene encoding N-cadherin, did not show any significant differences. The authors used qPCR on frozen hearts and reported no statistical differences between the different groups.

Lastly, the authors were interested in vinculin as this protein is also located at ICDs and plays a role in DCM. Vinculin immunostaining was not conclusive as the signal was weaker than that of N-cadherin while ICD immunostaining was vague. Further investigations are warranted.

The authors concluded that ICD disorganization is a characteristic of DCM and that ICD collapse may affect cardiac contractility and disease manifestation. They further concluded that the immunohistochemistry of N-cadherin is useful for identifying this feature.

There were, however, several limitations to the study that the authors themselves acknowledged. First, the number of heart samples was very small. For instance, only 5 hearts in the DCM group were used in the study, and the reason for reporting on only 5 hearts was not convincing. Clearly, further confirmation by other groups is warranted. Second, and this a major limitation that needs further clarification, is that the authors did not include all known DCM representatives of DCM etiology. The authors should have used different DCM hearts and reported their finding. Third, the method used for the ICD investigation was clearly a limitation and other less empirical methods of investigation could have been used.