in patients with subdural hematomas (4 of 48 patients; 8.3%) and consisted of significant increase in subdural hemorrhage with clinical deterioration; no rehemorrhages occurred in other types of intracranial hemorrhage (0 of 61 patients; 0%) (p = 0.04). No rehemorrhages occurred in the 32 patients who had neurosurgical intervention for their initial hemorrhage, compared to 4 recurrent hemorrhages in the 77 patients without neurosurgical intervention, but this difference was not significant (p = 0.32).

All rehemorrhage events occurred during anticoagulation resumption after ≤7 days of anticoagulation interruption, while less than one-half of the thrombotic events occurred during an anticoagulation interruption of ≤7 days (Figure 1).

Both thrombotic and rehemorrhage events are relatively uncommon when anticoagulation is interrupted in mechanical heart valve patients with intracranial hemorrhage. While clinical decisions regarding anticoagulation interruption must be tailored to an individual patient’s clinical situation, a general strategy of interrupting anticoagulation for 7 to 10 days may minimize the risk of both thrombotic and rehemorrhage events. Mechanical heart valve patients with subdural hematoma may be a group with a higher risk of recurrent hemorrhage.

*Alexander C. Flint, MD, PhD
Ramesh Lingamneni, MD
Vivek A. Rao, MD
Sheila L. Chan, MD
Xiushui Ren, MD
Jasmeen Pombra, MD
J. Claude Hemphill III, MD, MAS
Robert O. Bonow, MD

*Department of Neuroscience
Kaiser Permanente, Redwood City
1150 Veterans Boulevard
Redwood City, California 94025
E-mail: alexander.c.flint@kp.org
http://dx.doi.org/10.1016/j.jacc.2015.07.063

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES


Pathology of Intercalated Discs in Friedreich Cardiomyopathy

Friedreich ataxia (FA) is best known for its neurological phenotype, but the most common cause of death is heart disease (1). The pathogenesis of FA cardiomyopathy includes failure to clear iron from myocytes, chronic inflammation, fiber necrosis, and scarring (2). On cross section, heart fibers are significantly enlarged and excessively lobulated (2). In the longitudinal dimension, the pathogenesis also involves modifications of intercalated discs (ICDs), the plasma membrane specializations that connect heart fibers end-to-end. Many proteins participate in the assembly of fascia adherens junctions, desmosomes, and gap junctions (GJs) within or near ICDs (3).

Paraffin-embedded heart sections of 15 FA patients with confirmed homozygous guanine-adenine-adenine trinucleotide repeat expansions (3 autopsies, 1 biopsy specimen, 1 explant) and 12 controls (all autopsies) were stained with antibodies to N-cadherin (Figures 1A and 1B), α-actinin, vinculin, and desmoplakin to visualize fascia adherens junctions and desmosomes and ZO-1 and connexin 43 to reveal GJs. N-cadherin reaction product was used to measure distances between ICDs (Figure 1B, inset) in sections of the left ventricular wall, right ventricular wall, and ventricular septum (VS). Strips of fixed VS were processed for ultrastructural visualization of ICDs (Figures 1C and 1D).

In FA, all ICDs revealed by immunohistochemistry (Figure 1A), toluidine blue staining (Figure 1C, inset), or electron microscopy (Figure 1C) were disorganized, discontinuous, fragmented, and hyperconvoluted. N-cadherin reaction product showed an overall paucity of ICDs (Figure 1A). Connexin 43 reaction product revealed disorganization of ICDs as well as lateralization to plasma membranes (not illustrated). Inter-ICD distances were significantly and uniformly greater across all heart sections in FA (76 ± 11 μm) than in controls (54 ± 10 μm; p <0.001, main effect of FA in analysis of variance), but did not correlate with age of onset or death, disease duration, or guanine-adenine-adenine trinucleotide repeat expansion. Distances between Z discs remained normal (Figures 1C and 1D).

The underlying mutation in FA causes frataxin deficiency, which may adversely affect ICDs and GJs before the onset of heart disease and perhaps prena tally. The critical step in the faulty assembly and
maintenance of ICDs may target the most important ICD protein, N-cadherin (4), and also cause reduced expression of other adhesion proteins. Incorrectly constructed ICDs may make FA hearts vulnerable to progressive secondary changes that ultimately lead to fatal cardiomyopathy. Although frataxin replacement may prevent cardiomyocyte necrosis, it is unlikely to reverse incorrect maturation of ICD that occurs long before clinical manifestations of FA cardiomyopathy.

R. Liane Ramirez, MS
Alyssa B. Becker, BA
Joseph E. Mazurkiewicz, PhD
Paul J. Feustel, PhD
Benjamin B. Gelman, MD, PhD
*Arnulf H. Koeppen, MD
*Research Service (151)
Veterans Affairs Medical Center

113 Holland Avenue
Albany, New York 12208
E-mail: arnulf.koeppen@med.va.gov

http://dx.doi.org/10.1016/j.jacc.2015.06.1355

Please note: Funded by Friedreich’s Ataxia Research Alliance, National Institutes of Health (grant number R01NS069454), and Neurochemical Research, Inc. Drs. David Lynch and Susan Perlman made available the heart biopsy sample and explant, respectively. National Disease Research Interchange (NDRI) provided the control specimens. NDRI is supported by National Institutes of Health (2 U42 OD011158). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES


