Remodeling of Gap Junctional Coupling in Hypertrophied Right Ventricles of Rats With Monocrotaline-Induced Pulmonary Hypertension

Mahmud Uzzaman, Haruo Honjo, Yoshiko Takagishi, Luni Emdad, Anthony I. Magee, Nicholas J. Severs, Itsuo Kodama

Abstract—The present study investigates the remodeling of gap junctional organization in relation to changes in anisotropic conduction properties in hypertrophied right ventricles (RVs) of rats with monocrotaline (MCT)-induced pulmonary hypertension. In contrast to controls that showed immunolocalization of connexin43 (Cx43) labeling largely confined to the intercalated disks, RV myocytes from MCT-treated rats showed dispersion of Cx43 labeling over the entire cell surface. The disorganization of Cx43 labeling became more pronounced with the progression of hypertrophy. Desmoplakin remained localized to the intercalated disks, as in controls. In RV tissues, the proportion of Cx43 label at the intercalated disk progressively decreased. Quantitative analysis of en face views of intercalated disks revealed a significant decrease in the disk gap junctional density in RV tissues of MCT-treated rats (control, 0.18 versus MCT-treated, 0.14 at 2 weeks; control, 0.16 versus MCT-treated, 0.11 at 4 weeks). Conduction velocity in RVs parallel to the fiber orientation was significantly lower (30.2% [n = 9]) in MCT-treated rats at 4 weeks than in control rats, whereas there was no significant difference observed in the conduction velocity across the fiber orientation between control and MCT-treated rats. The anisotropic ratio of MCT-treated rats (1.38 ± 0.10) was significantly lower than that of control rats (1.98 ± 0.12). These results suggest that RV hypertrophy induced by pressure overload is associated with both disorganization of gap junction distribution and alteration of anisotropic conduction properties. (Circ Res. 2000;86:871-878.)

Key Words: ventricular hypertrophy ■ connexin ■ immunohistochemistry ■ anisotropy ■ conduction

Ventricular hypertrophy is associated with an increased risk of cardiac arrhythmia and sudden death.1,2 In addition to changes in active membrane properties (ionic currents, pumps, and exchangers), alterations in the passive properties of the myocardium are implicated in the arrhythmogenic substrate of hypertrophied ventricles.3 Central to the determinants of the passive properties are gap junctions that form the low-resistance pathway for propagation of electrical impulse between cardiac cells.4,5 Gap junctions are composed of transmembrane proteins that belong to the connexin family. The principal gap junctional protein expressed in the ventricles of mammalian heart is connexin43 (Cx43).6,7 Immunohistochemical studies using anti-Cx43 antibodies in ischemic heart disease and hypertrophic cardiomyopathy have revealed marked alteration of Cx43 expression and distribution.7–9 Remodeling of gap junctions may thus be an important morphological factor in abnormal conduction properties of the diseased heart, but our knowledge of this process in cardiac hypertrophy remains limited.

In rats, a parental dose of monocrotaline (MCT), a pyrrolizidine alkaloid, is known to cause pulmonary hypertension within a few weeks.10 The pressure overload in turn results in right ventricular (RV) hypertrophy, leading to right-sided congestive heart failure within several weeks. This model is suitable for chronological investigation of remodeling of the gap junction because progressive RV hypertrophy can be produced in a short period without any significant pathological changes in the left ventricle (LV).11

In the present study, we investigated changes in gap junction distribution and organization in the RVs of hypertrophied rat hearts 1 to 4 weeks after MCT treatment with the aid of anti-Cx43 antibody labeling and confocal laser scanning microscopy. Both disaggregated myocytes and multicellular tissue preparations were used for the immunohistochemistry. The distribution and organization of desmosomes, junctions responsible for mechanical linkage of intermediate filaments between cardiac cells,13 were examined in parallel using an antidesmoplakin antibody. Morphological remodel-
ing of gap junctions observed in association with ventricular hypertrophy was then correlated with altered anisotropic conduction properties measured in RV myocardium.

Materials and Methods

Animals
MCT (60 mg/kg) was injected in 79 5-week-old male Wistar rats (Chubu-kagaku-shizai, Nagoya, Japan) to produce pulmonary hypertension.15 Saline was injected in 59 rats as controls. Hypertrophy was estimated by the heart-to-body weight ratio and by the weight ratio of the RV free wall to the LV free wall plus interventricular septum. All procedures were conducted in accordance with statutory Japanese regulations.

Preparation of Samples
For standard microscopy, ventricular sections were stained with hematoxylin and eosin (H&E). In addition, thin sections fixed with 2% glutaraldehyde were stained with toluidine blue. Single myocytes were isolated from ventricles13 and fixed with 2% paraformaldehyde. Cryosections of ventricles were prepared from 2% paraformaldehyde–fixed hearts for tissue immunolabeling.

Immunohistochemistry
For immunodetection of gap junctions and desmosomes, a mouse monoclonal anti-Cx43 antibody (Chemicon) and rabbit antidesmoplakin antiserum were used. The specificity of both antibodies has been demonstrated previously.13,14

After permeabilization (0.3% Triton X-100), quenching (0.1 mol/L NH4Cl), and blocking (3% normal goat serum/5% BSA), samples were incubated with anti-Cx43 antibody (1:200) or a mixture of anti-Cx43 (1:200) and antidesmoplakin (1:100) antibodies overnight. Primary antibody-bound Cx43 complexes were visualized by FITC-conjugated antimouse IgG, and desmoplakin complexes were detected by biotinylated antirabbit IgG and Texas Red–conjugated streptavidin. Samples processed without primary antibody served as negative controls.

The labeled samples were examined using a confocal microscope (BioRad MRC-1024). In addition to single-plane evaluation, optical section series were taken.

Quantitative Image Data Analysis
The proportion of Cx43 immunolabeling at the intercalated disks relative to overall Cx43 was quantified according to a procedure described previously.15 Three randomly selected fields from longitudinally sectioned tissue were analyzed using NIH Image 1.61 (NIH). The Cx43 gap junctional density in the intercalated disk area was estimated in projection images of transversely sectioned tissue (NIH). The Cx43 gap junctional density in the intercalated disk area was analyzed using NIH Image 1.61 (NIH).

Electrophysiological Study
Extracellular electrogamgs were recorded from the epicardial surface of an arterially perfused isolated RV free wall through an electrode array (7 × 7 mm) consisting of 64 pairs of modified bipolar electrodes at 36°C.18 The endocardial Purkinje network was ablated by phenol to eliminate the preferential conduction and spontaneous excitation. The local activation time was measured under regular stimulation, and maps of exciton spread were constructed. Conduction velocity (θ) was determined by linear regression of the isochrone distance versus activation time. Lines parallel and perpendicular to the fiber orientation were defined as the direction of longitudinal (L) and transverse (T) propagation, respectively.

Results

RV Hypertrophy in MCT-Treated Rats
Figure 1 shows a comparison of the heart weight to body weight (HW/BW) ratio and the tissue weight ratio of RV free wall to LV free wall plus interventricular septum (RV/LV+IVS) between control and MCT-treated rats. Fifty-six rats (6 control and 8 MCT-treated rats at 1, 2, 3, and 4 weeks) were used. The ratios in control rats were constant throughout the observation period, whereas the ratios in MCT-treated rats increased progressively. The HW/BW ratio and RV/LV+IVS ratio were significantly larger in MCT-treated rats than controls 3 and 4 weeks after injection. Ten MCT-treated rats were followed up for 5 weeks after injection. In the fifth week, 6 MCT-treated rats died, and the remaining rats showed physical signs of right-sided congestive heart failure.

Figures 2A and 2B show the representative change in macroscopic morphology after MCT treatment. The thickness of the RV free wall in the MCT-treated rat was markedly increased, whereas the LV wall thickness was unaffected.

We also estimated the extent of cell hypertrophy based on cell size data obtained from 6 rats (3 control and 3 MCT-treated rats at 4 weeks). Twenty-five myocytes were randomly selected from a cell suspension of each control rat, and 41 or 42 myocytes were selected from a cell suspension of each MCT-treated rat. The cell width of the MCT-treated RV
myocytes (45.0 ± 0.6 μm) was significantly larger than controls (28.9 ± 0.3 μm), whereas there was no significant difference in the cell length between the 2 groups (control, 133.7 ± 2.4 μm versus MCT-treated, 136.7 ± 1.5 μm) (ANOVA for hierarchical classification). The average length-to-width ratio decreased from 4.6 in the control myocytes to 3.0 in the MCT-treated myocytes.

**Standard Light Microscopy**

Standard light microscopy was used to assess histopathological features in 10 rats (2 control and 3 MCT-treated rats at 2 and 4 weeks) (Figures 2C through 2F). Minimal myofiber disarray was observed in RV tissue sections stained with toluidine blue, but the general anisotropic architecture composed of 3 myocardial layers was well preserved even 4 weeks after MCT injection.

**Distribution of Immunolabeled Gap Junctions and Desmosomes in Isolated Myocytes**

RV and LV myocytes isolated from 32 rats (4 control and 4 MCT-treated rats at 1, 2, 3, and 4 weeks) were labeled with anti-Cx43 and antidesmoplakin antibodies to study immunolocalization of gap junctions and desmosomes (Figure 3). In control RV myocytes labeled with Cx43 antibody alone, gap junctions were visualized as aggregates of bright punctate fluorescent domains at the cell termini, marking the positions of intercalated disks (Figure 3A). The staining often extended across the full width of the myocyte, but shorter punctate lines were also observed at the sites of bifurcations of the main cell body. Double staining for Cx43 (green) and desmoplakin (red) confirmed coexistence of gap junctions and desmosomes at the cell termini (Figure 3E). These patterns were common to myocytes from RVs and LVs.

The Cx43 staining patterns of RV myocytes from rats treated with MCT for 2 weeks and longer differed markedly from controls; the gap junctional labeling was no longer confined to the cell termini but showed varying degrees of dispersion over the cell surface (Figures 3B and 3C). Double staining (Figures 3F and 3G) clearly revealed that the dispersed Cx43 immunolabeling on the cell surface was independent from the disk-like structure at the cell termini composed of both desmoplakin and Cx43 labeling. The disordered patterns of Cx43 immunostaining tended to be-
come more pronounced with the progression of hypertrophy as assessed by increased cell width. The dissociation of Cx43 and desmoplakin labeling was also remarkable (Figures 3G and 3H). In contrast, ventricular myocytes isolated from the LVs of MCT-treated rats showed normal Cx43 labeling patterns (Figure 3D). The changes described on hypertrophied RV myocytes are particularly clearly illustrated in double-labeled aggregates (3 myocytes with lateral contact) obtained from control and MCT-treated (4 weeks) rats (Figures 3I and 3J).

Distribution of Immunolabeled Gap Junctions and Desmosomes in Tissue Sections

Immunolabeling of Cx43 and desmoplakin in ventricular tissue sections was carried out in 48 rats (6 control and 6 MCT-treated rats at 1, 2, 3, and 4 weeks). Figures 4A through 4D show the distributions of immunolabeled Cx43 gap junctions and desmosomes in single confocal optical slices through longitudinally sectioned RV myocardium. In control rats, Cx43-containing gap junctions are highly organized into clusters of fluorescent label at the intercalated disks running across the longitudinal axis (Figure 4A). Double staining of RV sections of control rats (Figure 4C) confirmed that the desmosomes are also confined to the disks.

In rats treated with MCT for longer than 2 weeks, the Cx43 staining was no longer confined to the intercalated disks (Figure 4B). Instead, the staining pattern showed varying degrees of dispersion over the cell surface. It was possible to identify the approximate position of the intercalated disks by the presence of aggregates of labeled junctions, but the amount of signal was less and its distribution was more irregular than controls. Double staining (Figure 4D) confirmed a marked dissociation of Cx43 from the disks as identified by desmoplakin labeling. A parallel myofiber arrangement was generally preserved in the hypertrophied myocardium, but constituent myocytes showed more complex and irregular configurations than control myocardium.

We estimated the proportion of Cx43 label in transverse array (at the position of intercalated disks) over the total label present in the 3 test fields from each RV tissue preparation sectioned longitudinally. The results obtained from 24 rats (6 control and 6 MCT-treated rats at 2 and 4 weeks) are summarized in Figure 4E. The proportion of Cx43 label at the intercalated disks was significantly lower in MCT-treated rats 2 and 4 weeks after injection. The proportion of desmoplakin label at the intercalated disks in RV myocardium was always greater than 90% in both control and MCT-treated rats (data not shown).

Figure 4 shows Cx43 immunolabeling in the intercalated disk area seen en face in RV tissues sectioned transversely. Images were taken at 1-μm intervals to cover a full thickness of the intercalated disk, and the entire series was projected as a single composite image. In the control tissue, there was a normal distribution of gap junctional label, with small central gap junctions surrounded by extensive larger spots of label at the disk periphery. In the tissues obtained from MCT-treated rats (for 2 to 4 weeks), the larger peripheral gap junctions were preserved, but there was a striking loss of the central smaller gap junctions, giving rise to a more empty appearance of the disks. We estimated the gap junctional density in the intercalated disk in 12 rats (3 control and 3 MCT-treated rats at 2 and 4 weeks) using a protocol reported by Kaprielian et al.16 Thirty intercalated disks in 10 fields were analyzed in each group (Table). The ratio of gap junctional area to the total disk area was significantly lower in MCT-treated rats (2 and 4 weeks) than in respective controls.
In the LV tissues, the normal labeling patterns of Cx43 were well preserved in MCT-treated rats even 4 weeks after injection (data not shown).

Immunoblot and Immunoconfocal Analysis

Western blotting was carried out in 12 rats (6 control and 6 MCT-treated rats at 4 weeks). The Cx43 antibodies recognized 3 bands migrating between 42 and 45 kDa (phosphorylated and nonphosphorylated states) on immunoblots from RV tissue homogenates of control and MCT-treated rats (Figure 6) as demonstrated previously. Densitometric quantification revealed no significant differences in the amount between control and MCT-treated rats. In line with the immunoblot analysis, the quantity of Cx43 signal per unit volume of RV myocyte (a total of 20 cells from each group) measured by quantitative immunoconfocal microscopy was not significantly different between control and MCT-treated rats 4 weeks after injection.

Anisotropic Conduction Properties

Anisotropic conduction properties in the epicardial surface of RV tissues were examined in 18 rats (9 control and 9 MCT-treated rats at 4 weeks) (Figure 7). Constant stimuli (2.5 Hz) were applied to the middle of the upper edge of the 64-channel electrode grid (≈1 mm below the atrioventricular groove). In controls (Figure 7A, top), the activation front proceeded at the highest speed in a direction parallel (longitudinal, L) to the subepicardial fiber orientation and at the slowest speed in a direction perpendicular (transverse, T). The isochrones showed an elliptical activation pattern indicating the normal uniform anisotropy. In the tissue from a rat treated with MCT for 4 weeks (Figure 7A, bottom), the elliptical isochrone pattern was less marked (more circular) because of a moderate slowing of L propagation. Figure 7B shows θ for L and T propagation and their ratios.

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conduction velocity parallel with the fiber orientation ($\theta_L$) in RV tissues from MCT-treated rats was significantly less than controls (30.2% on average), but there was no significant difference in conduction velocity across fiber orientation ($\theta_T$) between the 2 groups. The anisotropic ratio of conduction velocity ($\theta_L/\theta_T$) in MCT-treated rats (1.38±0.10) was significantly lower than controls (1.98±0.12).

**Discussion**

In the present study, we investigated remodeling of gap junctional coupling in hypertrophied RVs of rats secondary to MCT-induced pulmonary hypertension. The novel findings are that (1) immunolocalized Cx43 in hypertrophied myocytes is not confined to cell termini (intcalated disks) but shows varying degrees of dispersion over the entire cell surface; (2) there is a loss of the population of small gap junctions in the intercalated disk center of the hypertrophied myocardium, giving rise to a decrease in the disk gap junctional density; and (3) there is a decrease of $\theta_L$, whereas $\theta_T$ is preserved.

A variety of alterations in Cx43 gap junctions have been reported in previous studies on the hypertrophied heart. For example, globally reduced levels of Cx43 protein have been reported in immunoblot studies on ventricular hypertrophy in transgenic hypertensive rats and in immunofluorescence studies on chronically pressure-overloaded hypertrophied myocardium in humans undergoing surgical replacement of a stenosed aortic valve. On the other hand, no alteration in Cx43 transcript levels was detectable at the 4-week stage in the hypertrophied hearts of rats made hypertensive by renal artery clipping or deoxycorticosterone/salt administration, whereas elevated Cx43 protein was reported in the early phase of hypertrophy due to renovascular hypertension in the guinea pig. Thus, although altered Cx43 gap junctional expression seems well documented in hypertrophy, no single form of change common to all forms of hypertrophy has been identified. Factors contributing to this apparent lack of uniformity in the findings to date may include the use of different species, sampling periods, and models in which hypertrophy may develop at different rates.

The remarkable dispersion of gap junctions over the lateral surface of RV myocytes reported in the present study was not apparent in any of the above studies. This stage-dependent change in distribution, readily recognized 2 weeks after MCT injection and yet more prominent at 4 weeks, involved a marked and progressive decrease in the measured proportion of Cx43 labeling of intercalated disks but no detectable alteration in the global Cx43 content. This dramatic change in gap junction distribution shows some similarity to that seen in hypertrophic cardiomyopathy and at the border zone of the healed human myocardial infarct; but, in contrast to these situations, the changes observed in the present study were not associated with a major alteration in myocyte orientation or myofiber disarray. Because gap junctional disorganization can develop rapidly after acute myocardial infarction, it might be suggested that the changing gap junction distribution observed in the present study could similarly be attributable to acute cell injury arising directly from the effect of MCT. However, it was shown in our previous experiments that direct application of MCT (1 to 60 mg/L) caused no significant effects on action potential configuration and ionic currents (transient outward current and L-type calcium current) of rat ventricular myocytes. The conduction velocity in rat RV epicardial surface was also unaffected by direct application of MCT (Kodama I, Honjo H, Uzzaman M, unpublished observation, 1999). Moreover, the pattern of Cx43 gap junctions in the LV myocytes remained completely normal throughout MCT treatment. Hence, the altered Cx43 gap junction distribution observed in the RV myocardium is interpreted as a component of the extensive hypertrophic remodeling that occurs in response to pressure overload (pulmonary hypertension) rather than to direct toxic effects of MCT treatment.

In contrast to the appearance of extensive lateral Cx43 staining in remodeling RVs after MCT treatment, a reduction...
in lateral cell-cell contact has been reported in remodeling LV canine myocardium after infarction.\textsuperscript{28} The changes reported in the latter model were identified 3 to 10 weeks after infarction in selected areas of myocardium around the infarct scar that maintained a well-arrayed cell orientation, and the resulting predicted increase in resistance to transverse current flow was considered consistent with earlier electrophysiological findings.\textsuperscript{29} On this basis, it might correspondingly be predicted that increased lateral Cx43 staining, as observed in the present study, might lead to an increase in transverse conduction velocity. Our finding that the transverse conduction velocity remained unchanged in practice emphasizes that Cx43 protein distribution may not always directly reflect the distribution of functional gap junction channels. One possible explanation for the presence of extensive seemingly nonfunctional lateral Cx43 could relate to processes of gap junction remodeling. Lateral Cx43 staining in myocytes at the border zone of human infarcts is due at least in part to segments of internalized gap junction membrane,\textsuperscript{25} and our preliminary immunogold electron microscopic observations in the MCT model suggest that a proportion of the lateral Cx43 label is not associated with trilaminar gap junction structures. The presence of such features in the MCT model but not other models of hypertrophy may be due to the comparative rapidity and severity of the hypertrophic response in the former.

Cable theory predicts that as cell diameter increases, as occurs in cardiac hypertrophy, conduction velocity will increase. However, using isolated hypertrophied human myocardium, it has been found that a reduction of conduction velocity accompanies cell enlargement, and it was proposed that this is because of an additional increase of intracellular resistivity ($R_c$). Cooklin et al.\textsuperscript{3} measured the impedance to current flow in the intracellular compartment of guinea pig--hypertrophied LV myocardium prepared by aortic constriction. Their results revealed that an extensive LV hypertrophy is associated with an increased $R_c$, which can be attributed solely to an increase of the junctional resistance between adjacent cells.\textsuperscript{3} They explained the decrease in conduction velocity of the animal model by an inhibition of intercellular electrical coupling.\textsuperscript{2} Notwithstanding the need for caution in relating Cx43 distribution to electrophysiological properties, as highlighted above, one predicted effect of the decreased gap junctional density in the intercalated disk observed in the present study might be to reduce local current flow parallel with the myocardial fiber orientation. That reduced levels of Cx43 can result in slowed conduction has been demonstrated from studies on mice heterozygous for a null mutation of the Cx43 gene.\textsuperscript{25} In the hypertrophied RV free wall, in fact, the longitudinal conduction velocity decreased significantly, but the transverse conduction velocity was unchanged, giving rise to a significant reduction of anisotropic ratio in comparison with control preparations.

In conclusion, we have shown that RV hypertrophy induced by pressure overload is associated with alterations of anisotropic properties and altered distribution of Cx43 gap junctions. Whether a causal relationship exists between these changes requires further investigation.

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