HISTOLOGICAL STUDY OF PULMONARY ARTERY DENERVATION

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Abstract. Objectives: to evaluate the efficacy and safety of circular radiofrequency ablation of the pulmonary trunk and main pulmonary arteries in patients with severe pulmonary hypertension using a histological study. Materials and methods: for the analysis of autopsy material from non-operated patients, three study groups were identified. Experimental – with chronic pulmonary hypertension with mitral disease and radiofrequency ablation. Comparisons – with severe pulmonary hypertension and without radiofrequency ablation. Control – without pulmonary hypertension and radiofrequency ablation, who died from causes not associated with cardiovascular diseases. Hematoxylin and eosin staining according to Van Gieson was used to visualize the damage to the tissue samples of the vascular wall. The technique of impregnation with silver staining was used to determine the damage to the nerve plexuses and endings. Results: analysis of the results of optical density and the relative average area of argentophilic fibers revealed a decrease in these parameters in the ablation group. In patients of the comparison group, where a high level of pulmonary hypertension was also observed, there was a significant accumulation of argentophilic fibers. Conclusion: histological examination showed an increase in the formation of sympathetic nerves in the adventitia of the pulmonary arteries in severe pulmonary hypertension. The same pulmonary arteries denervation procedure is an effective and safe way of denervation of the sympathetic plexuses located in the adventitia layer of the pulmonary arteries, which is confirmed by histological studies.

Keywords: secondary pulmonary hypertension, pulmonary arteries denervation, ganglion plexus denervation, histological study.

List of Abbreviations

AF – atrial fibrillation
PA – pulmonary arteries
PADN – pulmonary arteries denervation
PAH – pulmonary arterial hypertension
PC – pulmonary circulation
PVR – pulmonary vascular resistance
RFA – radiofrequency ablation

Introduction

Diseases of the cardiovascular system continue to occupy a leading position among all human diseases. Therefore, scientific research aimed at reducing the incidence of the cardiovascular system remains relevant at the present time. In particular, the prevalence of mitral disease among the population reaches 8%, and numerous complications require an individual surgical approach in each case (Trofimov *et al.*, 2017).

Mitral diseases in their natural course primarily contribute to the dilatation of the left patrium, the development of congestion in the PC and the formation of secondary PH, disturbance of the electrophysiological characteristics of the myocardium with the appearance of pathological re-entry circles with the formation of AF, as well as the progression of comorbid pathology (Trofimov *et al.*; 2014, Medvedev *et al.*, 2015). AF is the most frequent arrhythmological complication in patients with valvular heart disease, reaching a value of 30–50%. Concomitant AF has a negative effect on the postoperative period of this category of patients, reduces the effectiveness of surgery, the quality of life of patients, significantly increases the risk of thromboembolic complications, promotes the progression of heart failure and, as a result, increases overall mortality (Zhurko *et al.*, 2017; Bockeria *et al.*, 2014; Babokin & Trofimov, 2019).

AF is one of the most common cardiac arrhythmias in the population; it reaches 2% and has been steadily increasing over the past 10 years (Sulimov & Lishuta, 2017; Trofimov *et al.*, 2015).

Definitely, for the successful treatment of AF, it is necessary to correct the valvular pathology of the heart. However, unfortunately, this is not enough in most cases – surgical treatment of mitral disease in patients with preoperative AF leads to restoration of sinus rhythm

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only in 8.5–20%, which requires additional surgical intervention. The natural course of mitral valve disease contributes to a progressive increase in pressure in the PH, which in turn leads to remodeling of the right heart with the formation of relative tricuspid insufficiency against the background of annulodilation of the fibrous ring of the tricuspid valve. All this directly affects the postoperative prognosis of patients, the quality and duration of life (Zheleznev *et al.*, 2016).

The modern interpretation of PH implies the presence of a group of diseases characterized by an increase in pressure in the pulmonary arteries and an increase in PVR, which increase the mortality of this category of patients (Galie *et al.*, 2016).

It is customary to isolate primary PH, mediated by the mutation of chromosome 2q33, which is responsible for the growth and proliferation of endothelial cells. Secondary PH develops in patients with systemic diseases, lesions of the left heart, metabolic disorders, pulmonary thromboembolism, and respiratory pathology (Porodenko *et al.*, 2014).

The pathogenesis of LH is represented by an imbalance of cellular metabolites of thromboxane and prostacyclin with an increase in thromboxane activity, a decrease in nitric oxide production, an increase in the synthesis of vasoconstrictors by endothelial cells, hypertrophy of smooth muscle cells with secondary vascular stenosis, thrombosis in situ, the reaction of adventitia and vascular intima in the form of increased proliferation (Gaine, 2000).

The current classification (2018) includes 5 main clinical phenotypes of PH: PAH; PH due to left heart disease; PH due to lung diseases and/or hypoxia; PH due to pulmonary artery obstructions; PH with unclear and/or multifactorial mechanisms (Simonneau *et al.*, 2013).

High PH levels in patients with valvular heart disease reduce the effectiveness of surgery, the rate of postoperative remodeling of cardiac cavities and also affects the preservation of sinus rhythm in patients with AF after the Maze IV procedure (Trofimov *et al.*, 2018).

The need for surgical treatment of severe secondary PH in patients with valvular heart disease was highlighted in the study by S. Briongos Figuero et al., where it was demonstrated that even after mitral defect correction, the initial high PH remained in the postoperative period (odds ratio 1.761; $p = 0.03$) (Briongos *et al.*, 2016). The histological substantiation of the existence of sympathetic nerve structures in the adventitia layer of the PA, which regulate the tone of the pulmonary arterioles and contribute to an increase in pressure in the PC, was first elucidated by a group of authors led by J. Osorio in 1962 (Osorio & Russek, 1962). Subsequently, these results were confirmed in the works of B.G. Baylen (Baylen *et al.*, 1980) and C.E. Juratsch (Juratsch *et al.*, 1980).

Modern methods of conservative treatment of high PH do not significantly affect the course of the disease in all patients and are associated with the use of drugs with high financial costs (Uazzi *et al.*, 2012).

A surgical method for the correction of severe PH was first proposed by S.L. Chen, which consisted of circular endovascular catheter ablation of the pulmonary artery trunk and the mouths of both PA. The immediate results of the surgery were encouraging and contributed to a significant reduction in pulmonary hypertension (Chen *et al.*, 2013).

Subsequently, several research papers were presented on the surgical treatment of PH in patients with mitral valve pathology, carried out during cardiac surgery with artificial circulation. The technique of using a monopolar electrode for radiofrequency ablation of the anterior wall of the trunk and the orifices of the PA is described (Bogachev-Prokofiev *et al.*, 2019). Currently, a study on the use of a bipolar clamp-ablator for performing circular pulmonary denervation is also underway (Trofimov *et al.*, 2017; Trofimov *et al.*, 2019). Despite the active search for surgical methods for correcting PH, the problem of effective treatment of high secondary PH remains relevant because generally accepted recommendations for the treatment and application of existing methods have not been developed, and there is no histological evidence of the applied radiofrequency effect on the PA walls during cardiac surgery.

Materials and Methods

The study has been approved by the local ethical committee. All the studied patients before the operation, without fail, were informed about the upcoming additional procedure PADN, which was planned to be performed with the main stage of surgical correction, signed informed voluntary, according to the principles of clinical practice (Good Clinical Practice – GCP), in accordance with the Helsinki Declaration.

In the course of the research work, autopsy material of the pulmonary trunk with its right and left branches of the PA was taken from patients, from the moment of biological death of which no more than 3 hours had elapsed (Fig. 1).

The circularity of the radio-frequency effect on the samples under study was achieved due to their tight flat fixation in the jaws of the ablator clamp.

After compression of the artery samples, a controlled radio-frequency effect on the vessel walls was performed using electrodes built into the jaws due to the energy supplied from an automatically programmed hardware generator (Fig. 2).

During the ablation procedure, continuous hardware monitoring of the degree of tissue conductivity was carried out with automatic calculation of the impedance and displaying it in a dynamic graphical form with, inter alia, the calculated boundaries of the estimated level of transmural tissue damage.

Two ablation applications were performed on the pulmonary trunk and separately on the orifices of each PA, with the formation of 6 ablation lines, macroscopically visualized in the form of imprints, including those from mechanical impact, on the outer surface of the PA vessels (Fig. 3).

The study involved dividing the autopsy material of the pulmonary artery taken from 9 non-operated patients into 3 comparison groups, 3 patients in each group. The first experimental group included histological tissues of patients with chronic PH, formed against the background of mitral disease. Samples in this group were subjected to circular ablation treatment (207 histological samples). The second, comparison group, included material from patients with high PH, on which ablation was not performed (24 histological samples).

The third, control group, included material from patients who did not have PH and whose cause of death was not cardiovascular pathology. These samples were not exposed to radiofrequency (35 histological samples).

Subsequently, from all samples of the PA wall, two sections were formed, in each of which 6 fields were allocated for visual analysis, and then, as the optical density was determined, up to ten repeated calculations were additionally performed for each field of view. After RFA exposure to the aircraft material, all samples were fixed in a 10% solution of buffered neutral formalin. All the material to be fixed was in a solution, the volume of which was 10 or more times the volume of the material itself. The samples were processed in solution for 36 hours at room temperature.

During ablation exposure, fixation of the PA in the flat parallel branches of the clamp-ablator during tissue spreading after transverse clamping, forms conditional «edge zones» in which the applied mechanical action also has a «tearing» effect (Fig. 4), which will be reflected further.

Therefore, based on the unevenness of such lateral mechanical compression, the material from the first group, depending on the area of the ablated tissue, was further divided into two subgroups. Group 1A included areas of the central zone of the PA cross section (108 histological samples). Group 1B included areas of the «edge zone» (99 histological samples).

Subsequently, with the help of light microscopy and methods of staining the formed complexes, signs were identified that indicate the carried-out radio frequency exposure. With the help of staining with hematoxylin and eosin, typical general pathological processes were recorded. The color according to Van Gieson determined the transmurality of the impact. And impregnation with silver salts, according to Santiago Ramon-y-Cajal (Lillie, 1969), was used to visualize reticulin fibers, trunks and endings of peripheral nerve fibers.

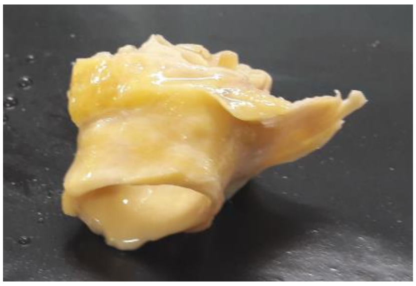

Fig. 1. Sample of a PA specimen with branches used for the study

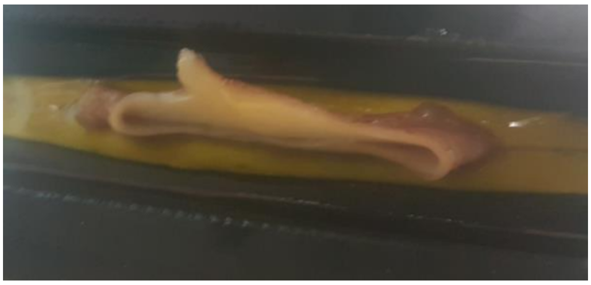

Fig. 2. Ablation of the pulmonary artery witha clamp-ablator in the experiment

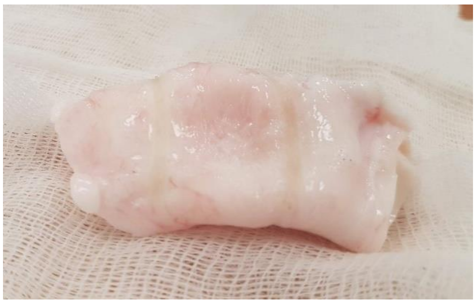

Fig. 3. Ablation lines formed on the outer surface of the samples after the RF exposure in the experiment

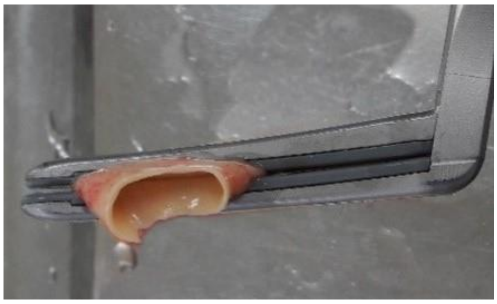

Fig. 4. Scheme of fixing the walls of the aircraft in the branches with their transverse clamping

The degree of thermal ablation exposure was assessed using a semi-quantitative analysis, calculated for ten fields of view, of all identified pathological processes. The possibility of their mathematical assessment was carried out through the use of computer morphometry attached to photographs of sections of preparations obtained with an Olympus SP350 camera in the optics of a Leica CME microscope.

The statistical evaluation of the results was calculated using the SPSS Statistics 26 software. To describe the quantitative data, the mean and standard deviation ($M \pm \sigma$) were used. To test statistical hypotheses in the presence of a normal distribution of the initial data, the Student's t-test was used, and in the case of unequal variances, the Mann–Whitney U-rank test was used. When constructing contingency tables for comparison, the Kruskal–Wallis test (for quantitative and rank data) and Pearson's chi-square test (for qualitative data) were used to check the equality of the samples of all 3 groups. Differences were considered significant at $p < 0.05$ (Glantz, 1998).

In the study at the light-optical level, for comparison, the qualitative signs of the RFA exposure were determined after the assessment of histological samples of all groups of materials (Fig. 5).

So, from the side of the adventitia of the PA with the spread to the layer of the wall media, in sections transmurally, the fields of elastic fibers were determined with signs of their pronounced disorganization in the form of their thinning and rarefaction, which indicates the destruction of dense intercellular associations in the media of the vessel. In the presence of such changes in the structure of fibroblasts and smooth myocytes, the phenomena of karyorrhexis and karyolysis were determined.

In addition, in some areas of the subendothelial layer among the areas of fibrinoid necrosis, foci of metachromasia were detected. This may indicate a lesser degree of RF energy distribution in this layer.

In general, after RFA, deep transmural disorganization of the tissues of the PA wall was observed (Fig. 6).

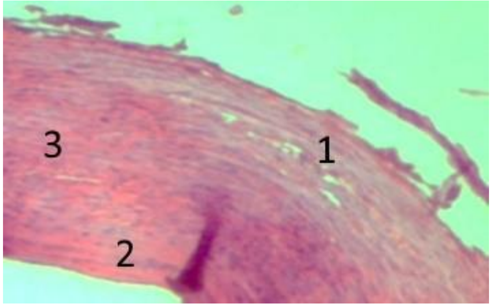

Fig. 5. «Edge zone» (group 1B) of a cross section of the ablation site (magnification x40, staining with hematoxylin and eosin). Designations: 1) under the adventitia membrane – thinning of elastic fibers, 2) necrosis in the subendothelial layer – fibrinoid necrosis, 3) foci of metachromasia

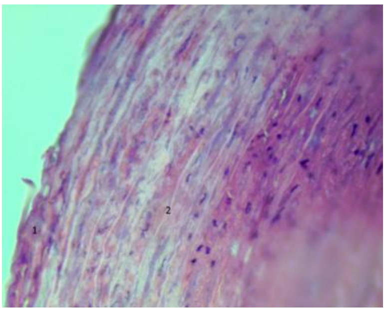

Fig. 6. Central section (group 1A) of the cross-section of the LA wall in the zone of radiofrequency exposure (magnification x400, staining with hematoxylin and eosin). Designations: 1) superficial mechanical desquamation in the adventitia layer, 2) the phenomenon of karyorrhexis and karyolysis (fibrinoid necrosis)

Fig. 7. «Edge zone» (group 1B) of the cross section of the ablation site (magnification x10, staining according to Van Gieson). Designations: 1) areas of fibrinoid necrosis under the adventitia 2) mechanical crushing of tissue in the subendothelial layer

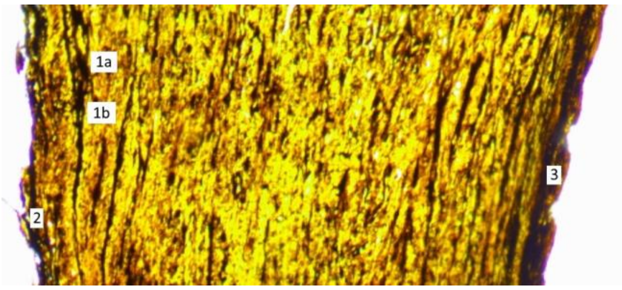

Fig. 8. «Edge zone» (group 1B) of a cross section of the ablation exposure area (magnification x100, impregnation with silver salts). Designations: 1) areas of metallic silver staining of nerve endings (a) and reticulin fibers (b), 2) adventitia, 3) subendothelial layer with silver deposits

To assess the depth (transmurality) of the thermal ablation effect, van Gieson staining was used (Fig. 7).

On tissue sections stained according to Van Gieson, as well as in staining with hematoxylin and eosin, areas of fibrinoid necrosis are determined, located directly in the area of contact of the electrode surface of the jaws of the clamp-ablator to the adventitial layer, which is due to the action of the radio frequency current, and in the subendothelial the layer of the "edge parts" of the vessel - the zone of tissue crushing due to the bursting action of the applied mechanical compression.

The impregnation of samples with silver salts made it possible to determine pathological changes in argyrophilic fibers (Fig. 8).

A decrease in the density of the content of nerve tissue in the outer layer adjacent to the electrodes demonstrates the positive effect of radiofrequency denervation action on sympathetic nerve fibers after PADN.

Results

To conduct an intergroup analysis of histological results, a table was formed with scoring for each characteristic for all study groups (Table 1).

When studying the visual fields and scoring, pathological signs in the form of fibrinoid necrosis, metachromasia and pronounced uncoupling of collagen fibers were most densely observed in group 1B, which is explained by the creation of zones of tension, as a result of almost complete bending of the formed duplication of the PA walls due to the compression performed by the ablator branches.

In the other two groups (comparison and control), no signs of significant pathological disorganization of PA tissues were observed, and the density of nerve tissue structures impregnated with silver salts (reticulin fibers, trunks and endings of peripheral nerve fibers) was determined to be the highest among all samples.

In all samples of groups with performed thermal ablation, uneven staining of the PA wall structures with silver salts with a smaller distribution closer to its adventitial layer was noted, which may be due to the development of pathological changes in the structures of both reticulin and nerve fibers after the RF exposure.

To quantitatively reflect the density and the degree of distribution of the radiofrequency exposure, the pathological signs determined, including in the samples of the comparison and control groups, were evaluated morphometrically (Table 2).

To compare the degree of disorganization of the fibrous structures of the vessel media, the optical density index was calculated, equal to the decimal logarithm of the difference in light transmission through the object. The average optical density of the samples of the ablation group was significantly lower than in the comparison and control groups ($p < 0.001$), despite the presence of differences in the degree of disorganization of the fibrous structures of the connective tissue of the middle layer of PA between the samples of subgroups (group 1A – 0.1665 ± 0.0025, group 1B – 0.1505 ± 0.0022). When calculating the specific area of connective tissue uncoupling, its average value in the samples of the central part (group 1A) was 30%, and in the samples of the «edge part» (group 1B) – 43.2% of the tissue area in the field of view. The development of such a patho-logical sign is due to the pronounced mechanical compression of tissues by the jaws of the clamp-ablator, with a greater severity in the «edge zones» of the sections due to the bending of the LA walls and practically bursting of the fibrous structures of the wall.

Table 1

Semi-quantitative analysis of pathological signs of thermoablation exposure (points)

Pathological sign	**Ablation group**		**Comparison group (n = 24)**	**Control group (n = 35)**
	1A (central part, n = 108)	**1B (edge part, n = 99)**		
Fibrinoid necrosis	3	4	1	0
Metachromasia	2	4	0	0
Dissociation of collagen media fibers	3	5	0	0
Reticulin fibers, trunks and endings of peripheral nerve fibers	3	2	5	4

Table 2

Comparative assessment of the density and degree of distribution of the determined pathological signs

Pathological sign	Ablation group 1A (*n* = 63)	Ablation group 1B (*n* = 45)	Comparison group (*n* = 24)	Control group (*n* = 35)
Average comparative optical density of the aircraft wall (M ± σ)	0,1665* ±0,025	0,1948* ±0,029	0,8785* ±0,13	0,3326* ±0,05
Average specific area of argentophilic fibers (p ± σp%)	56,34±3,1*	57,75±2,7*	73,1±2,1*	65,81±1,8*
Average value of the specific area of connective tissue disorganization (p ± σp%)	30±4,2	43,2±1,9		

The values of the average area of argentophilic fibers in the ablation subgroups did not differ significantly, but the difference in indicators with the comparison and control groups was determined in the form of a lower percentage of argentophilic fibrous structures ($p < < 0.05$). At the same time, the highest concentration of argentophilic structures was determined in the comparison group, the samples of which, as in the ablation group, were taken from patients with high PH, but were not exposed to radiofrequency exposure. Disorganization of the fibers of the middle sheath of the PA in the study groups with the per- formed ablation was constant and weakly variable. Much less deposition of silver salts was observed in the adventitia layer and structures of the aircraft wall close to it, which were exposed to radio frequency exposure. In this case, the mechanical compression by the jaws did not affect the distribution of impregnation.

Discussion

Thus, based on the qualitative and quantitative analysis of the determined pathological signs in the samples of all groups, it was possible to distinguish changes that characterize the distinctive features of the performed thermoablation treatment in the form of varying degrees of severity of connective tissue disorganization, with the presence of fibrinoid necrosis in the subadential layers with a large impact, and the development of mucoid swelling, in the subendothelial layer – with a smaller one. In the «edge zones» of impact, due to a more pronounced mechanical compression, the described features are found over a larger area and have a deeper character with a distribution up to the intima.

Taking into account the circularity of the distribution of sympathetic nerve plexuses in the adventitia of the wall in the region of the trunk and bifurcation of the PA, for high-quality denervation, the application of thermal ablation energy is required evenly along the entire circumference of the treated adventitia, without affecting the deep layers, with vasoconstrictor sympathetic nerve fibers located in them. It should be remembered that, like other large pulmonary vessels, the region of the trunk and bifurcation is a strong reflexogenic zone participating in the neuroreflex regulation of the work of the vessels of the PC. This regulation is carried out by baroreceptors distributed in the intimate layer of the main branches of the PA. Activation of baroreceptors, which occurs with an increase in intravascular pressure in the PA, due to a decrease in the frequency of heart contractions and vasoconstriction in the systemic circulation, leads to a decrease in pressure in the systemic circle and the deposition of blood in the body, which ultimately reduces venous return to the heart and blood vessels of the lungs (Parin reflex). The Parin reflex plays a huge role in unloading the vessels of the pulmonary circulation, protecting the right ventricle from overload and preventing decompensation of the PC, including the development of acute pulmonary edema. Therefore, trauma to the intimate layer of arterial vessels will have a negative impact on the work of one of the compensatory mechanisms activated in patients with the development of PH.

Conclusion

Based on the results of histological analysis of autopsy material of PA samples, the effectiveness of radiofrequency exposure to the procedure for denervation of the PA in patients with severe PH was assessed. Comparison of material from 3 groups was carried out: from patients with high PH, with mitral heart disease, with ablation; from patients with high PH, on which ablation was not performed (comparison group); and from non-ablated patients without PH (control group). To determine the nature and depth of the thermal ablation effect, staining with hematoxylin and eosin and according to Van Gieson was used. And impregnation with silver salts was used to visualize damage to reticulin and nerve fibers.

The assessment of the degree of damage to the vascular wall was carried out on the basis of the totality of the observed pathological processes (fibrinoid necrosis, metachromasia, karyorrhexis and karyolysis, fibrinoid and mucoid swelling, lipid presence). And impregnation with silver salts made it possible to visualize damage to reticulin fibers, trunks and endings of peripheral nerve fibers. The average optical density of the samples in the ablation group was significantly lower than in the comparison and control groups ($p < 0.001$). When calculating the specific area of connective tissue uncoupling, its greater value was determined in the «edge zones» of the sections due to pronounced mechanical compression in these areas ($p = 0.056$).

The values of the average area of argentophilic fibers of the samples of the ablation group differed from the comparison and control groups in the form of a lower percentage of argentophilic fibrous structures ($p < 0.05$). In addition, the comparison group had the highest concentration of argentophilic structures, which indicates a higher content of nerve fibrous structures in patients with high PH. The effectiveness is confirmed by the results of histological analysis in the form of a lower (by 16%) content of argentophilic fibrous structures in tissues ex-posed to radiofrequency compared to untreated ones ($p < 0.05$).

Thus, radiofrequency denervation leads to the destruction of the sympathetic ganglia in the adventitial layer of the PA, which are responsible for the spasm of the precapillary bed of the PC in patients with a severe of PH.

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