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Fibrosis as a contributing factor to the induction of ventricular arrhythmias

Włóknienie jako czynnik sprzyjający powstawaniu komorowych zaburzeń rytmu serca

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INTRODUCTION

In the cardiac muscle, myocytes are tightly surrounded by a dense network of connective tissue, mostly built of collagen fibres, known as the extracellular matrix (ECM). Among the identified cardiac collagen isoforms, there are two major types: I and III that account for ~ 80% and ~ 20% of the total collagen, respectively. Collagen I forms relatively thick parallel extending fibres which are stretch-resistant and hardly

S u m m a r y

In a healthy heart, cardiomyocytes form a complex three-dimensional functional *syncytium* responsible for the contractile activity of the heart muscle. This complex structure is supported by a precise network called the extracellular matrix. It is mainly formed by collagen fibres and fibroblast cells. In the case of structural damage of the myocardium, for instance due to acute coronary events, the number and activity of fibroblasts increase, large amounts of collagen fibres are produced to fill up the gap resulting from cardiomyocyte death, create scar and thus preserve the integrity of the heart. Increased fibrosis also accompanies much less sudden processes than myocardial infarction, such as cardiac hypertrophy or ageing. Progressive fibrosis is associated not only with structural changes in the heart tissue, but also with the electrical function of the heart. Intensive fibrosis complicates the electrical impulse propagation, slows down conduction velocity, gives an opportunity to form unidirectional conduction blocks and increases the effectiveness of the spontaneously arising premature beats to evoke arrhythmias. This paper aims to summarise the current data concerning the cardiac fibrosis effects on the arrhythmic propensity of the heart.

S t r e s z c z e n i e

W zdrowym sercu kardiomiocyty tworzą sprzężoną funkcjonalnie, trójwymiarową strukturę odpowiedzialną za aktywność skurczową mięśnia sercowego. Ta złożona struktura jest stabilizowana przez macierz zewnątrzkomórkową. Ma ona postać sieci oplatającej kardiomiocyty, zbudowanej głównie z włókien kolagenowych i komórek zwanych fibroblastami. W przypadku nagłego ubytku kardiomiocytów, do którego może dojść w wyniku ostrego incydentu sercowego, wzrasta liczba i aktywność fibroblastów, dochodzi do produkcji dużej ilości włókien kolagenowych, w celu wypełnienia przestrzeni powstałej w wyniku śmierci kardiomiocytów. Powstaje łącznotkankowa blizna, dzięki której zostaje zachowana integralność mięśnia sercowego. Zwiększona produkcja włókien kolagenowych towarzyszy również przerostowi mięśnia sercowego lub procesowi starzenia. Postępujące włóknienie jest związane nie tylko ze zmianą struktury mięśnia sercowego i podatności rozkurczowej jego ścian, ale także ma istotny wpływ na czynność elektryczną serca. Zwiększone włóknienie komplikuje i wydłuża tor przewodzenia impulsu elektrycznego, spowalnia szybkość przewodzenia, sprzyja powstawaniu bloków przewodzenia oraz zwiększa skuteczność spontanicznie powstających przedwczesnych pobudzeń do wywoływania arytmii. Artykuł ma na celu podsumowanie aktualnej wiedzy dotyczącej wpływu zwłóknienia mięśnia sercowego na skłonność do występowania incydentów arytmicznych w sercu.

deformable. In contrast, collagen III forms a network of thinner, more flexible fibres, which are more susceptible to deformation than collagen I. Collagen III is the main component of the matrix that directly contacts cardiomyocytes. This means that this part of the ECM is easily distorted during the cardiomyocyte contraction-relaxation cycle. On the other hand, the fibres surrounding cardiomyocyte groups or layers are mainly built of collagen I, and therefore stiffer, which ensures

stability of the heart chambers geometry and prevents cardiac myocytes dislocation (1).

Collagen is synthesised by fibroblasts and released from the cells in the form of procollagen. As a result of proteolytic cleavage of C- and N-terminal fragments of the propeptide, final collagen molecule is formed. The three collagen molecules connect with each other forming triple helix as a final form of collagen fibre (2, 3). Finally, single fibres create a complex network of collagen fibres that surrounds cardiomyocytes. In a healthy heart of young individuals, this structure is rather thin, accounting for a small percentage (approximately 2%) of myocardial tissue. The main function of the extracellular matrix is to form a scaffold for cardiac myocytes, keeping them in the proper position. Moreover, ECM is responsible for controlling the extensibility of the heart muscle (collagen I), and transmission of contraction from the level of single cardiomyocyte to the whole heart (collagen III), controlling the proper functioning of the organ (4, 5).

Protecting the stable position of cardiomyocytes in the heart muscle by ECM is very important for the electrical activity of the heart, because it enables forming intercellular connections, making the proper propagation of the electrical excitation in the heart tissue possible. Intercellular conduction takes place through the gap junctions. One gap junction channel is composed of two connexons located in the cellular membrane of adjacent cardiomyocytes and forming together intercellular electrical connections, enabling propagation of excitation (6). Loss of electrical communication between the individual myocytes due to inappropriate amount or structure of ECM can cause conduction disturbances and eventually arrhythmias.

CARDIAC FIBROSIS

Myocyte necrosis occurs as a result of ischaemia, hypoxia or increased mechanical load. Mature heart has a very low regenerative capacity, therefore the general method of preserving the integrity of the structure of the heart muscle is to fill up the gap resulting from cardiomyocyte death with connective tissue (7, 8). Growth factors, cytokines, and hormones such as TGF- β , angiotensin II, endothelin-1, activate fibroblasts. Initiating and supporting mechanism of fibrosis and inhibit it, if necessary, by means of a feedback mechanism (9).

Increased collagen synthesis in the heart can also accompany the ageing process. In this case, however, collagen fibres penetrate between the strands of cardiomyocytes to form an intercellular cross-linking between them (10, 11). This process is associated with increased collagen synthesis, and thus, the quantity and thickness of fibres increase with age. Accumulation of the collagen fibres in the heart muscle tissue contributes to the stiffening of the structure of the ECM, to reduce the susceptibility of the myocardium to stretching and, consequently, to diastolic dysfunction. The exact mechanism of age-dependent fibrosis is unknown,

however, the process involves similar factors to the post-infarction scar formation. This phenomenon, however, differs significantly from the previously described mechanism of regeneration. First of all, it is not initiated as a consequence of death of cardiomyocytes, as happens in the case of fibrosis activated after myocardial infarction. Furthermore, there is a difference between the structure of fibrosis in both incidents. In the case of regenerative fibrosis, a compact scar of a limited area is formed in the place earlier occupied by cardiomyocytes. In the case of fibrosis associated with ageing, the heart tissue has to deal with the penetration of collagen fibres between cardiomyocytes, creating a connective cross-linking network.

Both regenerative fibrosis and fibrosis associated with the ageing of the heart muscle increase the risk of life-threatening arrhythmias influencing several components of the complicated mechanism of arrhythmia (12, 13).

THE ROLE OF FIBROSIS IN THE DEVELOPMENT OF ARRHYTHMIAS

The mechanism of life-threatening ventricular arrhythmias

Life-threatening arrhythmias include ventricular tachycardia and ventricular fibrillation and arise mainly in the re-entry mechanism. Most of such events are initiated by (1) ventricular extrasystolic beats (a trigger) that coexist with (2) favourable electrophysiological conditions (electrophysiological substrate: heterogeneous action potential duration (APD) and refractoriness and slow ventricular conduction velocity) (fig. 1). Thus, frequent ventricular extrasystolic beats and electrophysiological heterogeneity of the ventricular myocardium promote ventricular arrhythmias. Ventricular extrasystolic beats are triggered by early afterdepolarizations (EAD) that occur during the plateau phase or repolarization of the action potential and delayed afterdepolarizations (DAD) that occur after the completion of action potential. Abnormal intracellular Ca^{2+} handling (SR overload, uncontrolled Ca^{2+} leak from SR calcium channels, so called ryanodine receptors (RyRs), increased $\text{Na}^+/\text{Ca}^{2+}$ exchanged (NCX) expression and reduced SR calcium ATP-ase (SERCA)) is the main source of DAD. On the other hand, EAD results from increased APD caused by reduced function of potassium channels or increased function of calcium or sodium channels. Furthermore, heterogeneous prolongation of APD in adjacent groups of cells (dispersion of repolarization) can result in unidirectional block, initiating re-entry. Moreover, re-entry is favoured by slow conduction that can be caused by reduced AP amplitude and reduction of connexons responsible for cell-to-cell coupling. Excessive fibrosis affects both the arrhythmia substrate and the triggers. It facilitates the generation of a unidirectional conduction blocks, it contributes to the slowing down of the conduction velocity and makes the triggers more effective in initiating arrhythmia (fig. 1).

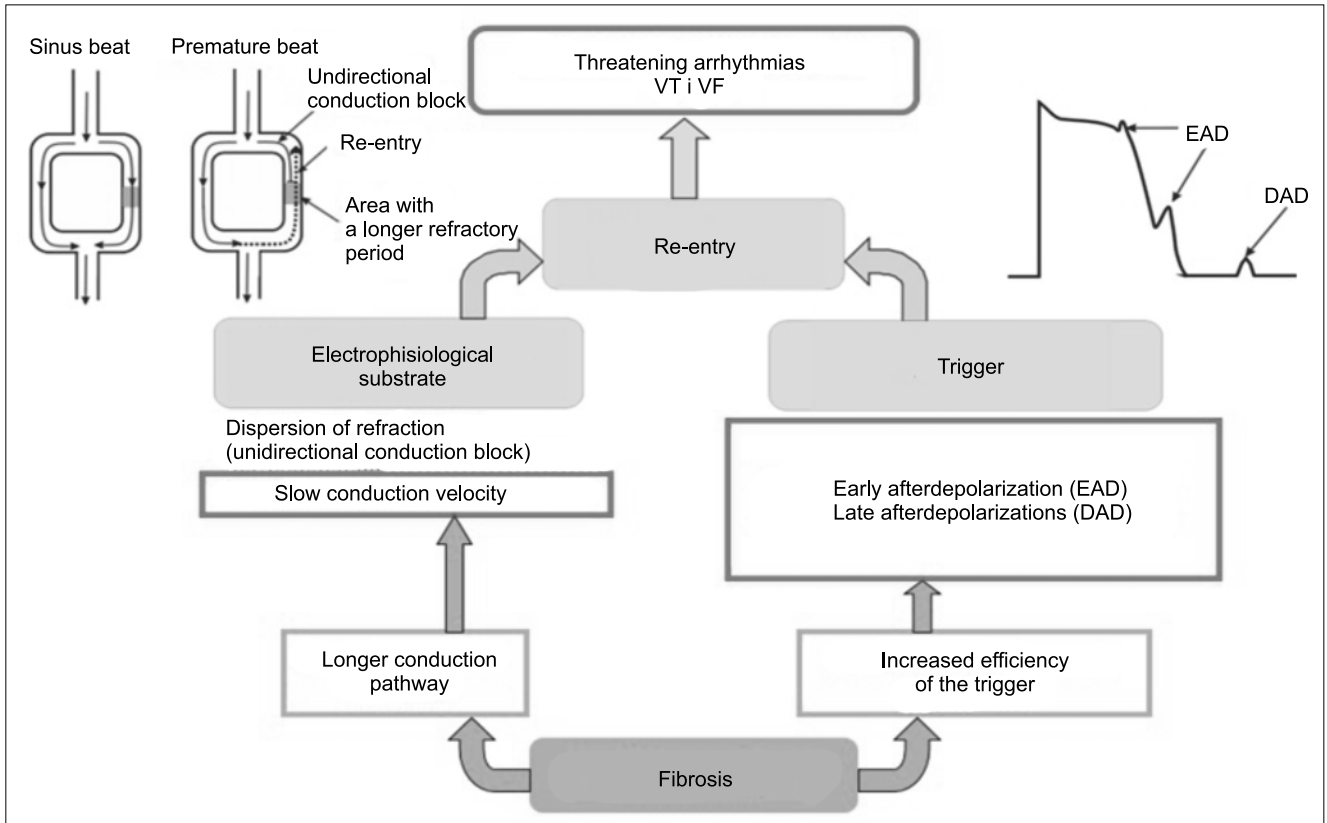


Fig. 1. The effect of fibrosis on the re-entry arrhythmia initiation and maintenance. Re-entry arrhythmia initiates when the trigger (e.g. early- or late-afterdepolarization, EAD and DAD, respectively) meets an appropriate electrophysiological substrate (dispersion of refraction, the main condition for unidirectional block occurrence or slow conduction velocity). Fibrosis influences both trigger and substrate making EAD and DAD more effective in arrhythmia initiation and slowing the conduction velocity due to lengthening the conduction pathway and reducing the amount of intracellular connections. In some conditions fibrosis may per se cause unidirectional block independently on dispersion of repolarization (sink-source mismatch phenomenon). The resulting re-entry may cause life-threatening arrhythmias: ventricular tachycardia (VT) or ventricular fibrillation (VF), which can lead to sudden cardiac death.

Fibrosis and unidirectional conduction block

The unidirectional conduction block is a precondition for the initiation of re-entry arrhythmias. The cardiac conduction pathway is complex. Each cardiomyocyte is electrically coupled with at least several other cardiomyocytes. Conduction takes place at a faster rate along the long axis of cardiomyocytes, but it is also possible along the short axis. Thus, the conduction pathway frequently splits up and then, after a certain distance, connect together (fig. 1). If the cardiomyocytes in the individual pathways have different refractory periods, it may result in the condition of premature beat appearance (especially in the condition of propagation of excitation in one pathway and blocking it in the other with longer refractory period).

As a result of the local block of conduction, excitation is propagated only in one pathway and when it reaches the point of two pathways connection, it can enter retrogradely the pathways previously blocked. This leads to the formation of a re-entry circuit (fig. 1, left panel).

Apart from the above, the unidirectional block may also form when the excitation created in the individual cardiomyocyte (source) has to be propagated to too many adjacent cardiomyocytes (sink). This phenomenon called sink-source mismatch (so little source, so

much sink) often occurs in a fibrotic heart. (15, 16). In these hearts, the fibrosis is mostly heterogeneous: areas of intensive fibrosis may contact the areas of almost unchanged tissue. During propagation of an excitation through the areas of intensive fibrosis, the signal travels through restricted by the collagen fibres, narrow pathway consisting of small number of electrically connected myocytes. At the junction of the fibrotic tissue with relatively normal composition, a single excited myocyte probably has to propagate electrical signal to more myocytes than in the area of fibrotic tissue. Thus, if an excitation attempts to be propagated from the tight strand of cardiomyocytes in an area of fibrotic tissue to the area of healthy tissue, the amplitude of excitation in the cardiomyocytes at the border between these areas may be too low for signal propagation and thus the unidirectional conduction block appears. On the other hand, when the excitation is propagated from numerous cardiomyocytes located in the area of normal tissue towards a reduced number of cells in a fibrotic tissue, the excitation may be easily retrogradely conducted, which promotes raising of re-entry circuit (17).

The effect of fibrosis on the conduction velocity

The intercellular conduction velocity is an important parameter for myocardial function. Effective conduction

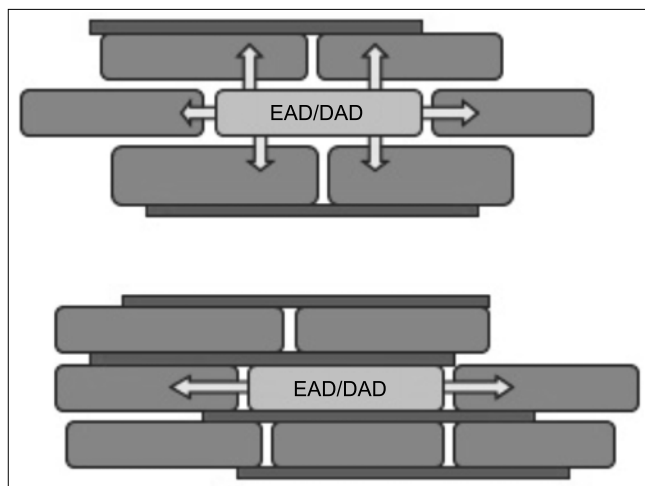


Fig. 2. Effectiveness of early- and delayed-afterdepolarization in arrhythmias initiation in healthy and fibrotic tissue. In healthy tissue (top panel), a myocyte generating afterdepolarization is usually connected to a number of neighbouring cells and afterdepolarization amplitude is too small to be transmitted to all coupled cells and thus it is suppressed. In a fibrotic tissue (bottom panel), the collagen fibres separate the individual myocyte from the majority of adjacent cells and therefore transmission of arising afterdepolarization to a lower number of coupled cells is more possible and may be transmitted at a longer distance. EAD – early afterdepolarization, DAD – delayed afterdepolarization.

ensures excitation of the ventricular cardiomyocytes during short time, which guarantees their synchronous contraction and adequate haemodynamic effect. On the other hand, conduction slowing results in dys-synchronous contraction and worsening of cardiac mechanics. Moreover, conduction abnormalities also predispose to the generation of reentrant arrhythmias promoting both induction and maintenance of re-entry circuit. The conduction velocity depends on the amplitude of the action potential, arising in excised myocyte, and the expression, distribution, and regulation of the connexin proteins. In a regular heart, connexons are located mainly on the end-to-end myocyte connections with their fewer number on the side-to-side connections resulting in a faster longitudinal conduction and effective impulse propagation. Intensive fibrosis makes the network of collagen fibres separate individual groups of cardiomyocytes reducing the number of cell-to-cell-coupling that results in slowing the inter-cellular conduction. Furthermore, the conduction pathway becomes more complex, which increases the time needed to excite all ventricular cardiomyocytes. Additionally, in the fibrotic tissue the gap junction remodelling induced changes in expression and location of ion channels contributing to the action potential, activation, particularly those located at the end of the cells. This leads to the decrease in amplitude of the action potential, which together with the quality of myocyte coupling is an important determinant of the conduction velocity.

The effect of fibrosis on the arrhythmic trigger

Fibrosis of the heart muscle affects the effectiveness of arrhythmias initiation by the triggers. As it was men-

tioned earlier, the main triggers of reentrant arrhythmias are EADs and DADs, the spontaneous afterdepolarizations generated additionally to appropriate action potential. If their amplitude is high enough, they can stimulate adjacent myocytes and initiate a premature beat, the main trigger of re-entry circuit (19). In a healthy heart, afterdepolarizations are usually generated locally and are not conducted at a longer distance due to the multidimensional structure of myocardium with individual cardiomyocytes surrounded by dozens of tightly-coupled cells. The amplitude of afterdepolarization is not high enough to excite all these myocytes (sink-source mismatch: so little source, so much sink). Thus, in the case of a normal tissue with tight cell-to-cell coupling, the majority of afterdepolarizations are suppressed and do not induce arrhythmias (fig. 2).

In contrast, in a fibrotic tissue, groups of cardiomyocytes are separated by a network of collagen fibres and therefore an individual cardiomyocyte is electrically coupled with a smaller number of adjacent cells. Thus, the afterdepolarization arising in such an environment much more likely excites adjacent cells than in a healthy tissue. In a narrow strand of cardiomyocytes it may propagate at a longer distance, induce unidirectional block, and finally arrhythmia.

Using computational modelling, it has been calculated how many cardiomyocytes should simultaneously develop afterdepolarization to ensure its propagation in a hypothetical one-dimensional structure of the tissue (cells arranged in series imitating the cardiomyocytes in a highly fibrotic tissue) and in a three-dimensional tissue (healthy tissue with normal EMC). The calculated number was 70-80 cardiomyocytes and 700-800 thousand cardiomyocytes in one-dimensional and three-dimensional tissue, respectively (20, 21). Transferring this data from models to the organ level leads to a conclusion that intensive fibrotic lesions may change physiologically the three-dimensional structure of a healthy heart muscle to the one-dimensional strands of cardiomyocytes separated from neighbouring cells by collagen fibres. Thus, induction of arrhythmias by common triggers such as EADs and DADs is much more likely in the highly fibrotic than in normal heart tissue.

THE PROPENSITY TO ARRHYTHMIAS AND THE TYPE OF FIBROSIS

So far, four types of myocardial fibrosis were distinguished: interstitial, compact, diffuse and patchy (22). Depending on the type of fibrosis, the electrical impulse propagation may be affected in two ways: the conduction velocity may slow down or a local unidirectional conduction block may ensue. The consequences of these two phenomena include increased likelihood of dangerous re-entry arrhythmias.

Compact fibrosis typically found in the post-infarcted hearts is characterised by the accumulation of connective tissue in a limited area deprived of the cardiomyocytes. This is the mildest form of fibrosis with regard to

the effectiveness of arrhythmia induction. In this case, the collagen fibres accumulating in the limited area do not significantly affect both the rate of impulse propagation and the formation of the unidirectional block. In spite of that fact, this type of dense fibrosis may act as an anatomical obstacle for propagated impulse and change the conduction pathway enabling the induction of reentrant circuit, but the phenomenon is neither typical nor frequent.

Diffuse fibrosis may result from myocarditis or hypertrophic cardiomyopathy. In this type of fibrosis, the collagen fibres are relatively short and appear among the cardiomyocytes. However, due to the length of the fibres, the contact between the individual myocardial cells is not substantially prevented. It has been demonstrated that scattered fibrosis reduces the number of connections mainly in the short ends of the cardiomyocytes promoting their translocation to the long side of the cell, increasing the anisotropy of conduction, which may facilitate re-entry formation. Moreover, reduction in the number of gap junctions may cause the dispersion of the action potential duration among the cells and unidirectional conduction block, but as in the case of a compact fibrosis, it is not a frequent phenomenon (23, 24).

Interstitial fibrosis and patchy fibrosis prevalent in failing hearts result in a more complex structure of the connective tissue. The long collagen fibres divide the layers of the myocardial cells. In the case of interstitial fibrosis, the collagen strands extend mainly along the muscle fibres, while in the patchy fibrosis, the collagen fibres are located randomly. They separate myocytes and substantially reduce connections between them (25, 26). It creates long, often zigzag conduction pathways, which often results in slowing the conduction velocity, dispersion of refraction and, therefore, re-entry generation. In both cases, such types of fibrosis are strongly arrhythmic (10).

MYOCYTE-FIBROBLAST COUPLING AND ARRHYTHMIC RISK

In a healthy heart, the number of fibroblasts is 2-3 times higher than cardiomyocytes (11). These small, spindle-shaped cells are located in the ECM, connect with each other via filopodia, and thus, form a kind of functional syncytium (27, 28). Fibroblasts synthesise collagen and metalloproteinases responsible for its degradation, thus control the synthesis, degradation and re-building of ECM (29).

In various pathologies, the activation of the fibrotic pathways rely on the activation of fibroblasts and their transformation into myofibroblasts, producing large amounts of collagen (31) and leading to the excessive fibrosis, a condition increasing the propensity to arrhythmias in at least several, mentioned above, mechanisms.

Interestingly, many studies have lately shown that fibroblasts may also directly control the cardiomyocyte electrical function and thus influence the arrhythmic

susceptibility of the heart (30). It has been shown that myofibroblasts in addition to the production of collagen, secrete cytokines, growth factors and hormones, such as TGF- β 1, endothelin-1, angiotensin II (32-36). These factors may affect the electrical function of cardiomyocytes by blocking the ion channels, such as sodium and potassium ones, resulting in changes in the action potential duration and decreasing its amplitude, which may promote afterdepolarizations and cause slowing of the conduction velocity, respectively (37-42).

Instead of the biochemical influences, mechano-electrical coupling between fibroblasts, myofibroblast and cardiomyocytes has been proved to possibly influence the electrical function of cardiomyocytes. Firstly, studies indicate that heterogeneous gap junctions composed of connexin 43 and 45 exist between cardiomyocyte and fibroblasts. Secondly, fibroblasts located in the close proximity to the cardiomyocytes undergo cyclic compression during their contractile shortening and thickening. As a result, the fibroblast membrane is stretched, which leads to the activation of mechano-sensitive ion channels and finally to fibroblast depolarization (43). The resting potential of the fibroblasts is about 40mV, which is much less negative than that of cardiomyocytes (-85mV). Due to the electrical connections via heterogeneous connexons the resting potential of fibroblasts and myocytes tends to equate. *In vitro* studies show that that connection results in less negative value of the cardiomyocyte resting potential (44). This may lead to the slowing of the conduction velocity or promoting afterdepolarizations and finally to reentrant arrhythmias (45). This hypothesis needs to be confirmed in the *in vivo* models, however it is conceivable that fibroblasts, influencing the electrical function of cardiomyocytes, may have direct impact on the generation of arrhythmias in the heart.

CONCLUSION

Fibroblasts play a central role in the process of maintenance of the normal structure of the ECM, a necessary scaffold for cardiomyocytes. Keeping cardiomyocytes in the right position ensures their proper connection and efficient propagation of electrical pulses. In the pathological conditions, involving necrosis and apoptosis of muscle cells, the number of fibroblasts increases and some of them are transformed to myofibroblasts. The synthesis of collagen increases to fill the emptied areas. This process is known as fibrosis. In addition to the positive aspects of this phenomenon, such as maintenance of the integrity and stability of the heart muscle, intensive fibrosis is also associated with the negative effects associated with the increase in the propensity to arrhythmias. Numerous collagen fibres separate individual myocytes as well as their strands and layers, destroying precise three-dimensional structure, resulting in changes in the conduction pathway and slowing the conduction velocity. Separation of individual groups of

cardiomyocytes also enhances the efficacy of the arrhythmia initiation by spontaneously generated afterdepolarizations.

Increased number of cardiac arrhythmic events results not only from the excess of collagen fibres. *In vitro* studies showed that the fibroblasts may directly interact with cardiomyocytes influencing their electrical activity, thus contributing to the initiation of arrhythmias.

Results of the discussed studies shed light on the fibroblasts as an extremely important players in the process of initiating arrhythmias, determining both the amount of connective tissue and the electrical function of cardiomyocytes. Thus, controlling the fibroblast function and their interactions with cardiomyocytes may contribute to the prevention of arrhythmias in a number of diseases of the cardiovascular system as well as in the ageing process.

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