Myocardial dissynergy and arrhythmia were compared as consequences of reperfusion after controlled ischemia (ligature of the left coronary artery) in fourteen dogs. Echocardiographic contrast agent administered in the aorta and two-dimensional echocardiography enabled images of the perfusion area. Reperfusion was established after 1, 2, 5, 10 and 15 min, and we analyzed the establishment of segmental wall motion (by echocardiography) and the appearance of reperfusion arrhythmias. After occlusion of the left coronary artery, the period for establishment of blood flow was on average, 1.24±0.4 min. When establishment of the coronary flow was accompanied by reperfusion arrhythmias, these developed on average 6.44±2.3 min. after reperfusion; minimally 2 min. and maximally 15 min from the end of interruption of the circulation. The establishment of ischemic region motion showed the slowest recovery (12.26±4.4 min).

Wall motion of the left ventricle after the short term of occlusion (1.0 min) appeared immediately after the establishment of blood flow. When the period of occlusion was longer (15 min), wall motion was achieved half an hour after reperfusion commenced (33.7 min). Left ventricle wall motion abnormalities are, in most cases, a sign of coronary circulation damage, they appear as a first manifestation of ischemia, but they recover slowest after reperfusion is established. Reperfusion arrhythmias do not always follow reperfusion, and if present, appear before left ventricle segmental wall motion is established.

Key words: echocardiography ischemia, reperfusion, left ventricle, wall motion, arrhythmias, dogs.

INTRODUCTION

Dysfunction of the left ventricle is one of the fundamental aspects of the myocardial ischemic process. Regional myocardial dissynergy is a specific indicator of ischemia and is rarely observed in other states. As regional dissynergy follows perfusion deficit, in the detection of ischemia the functional abnormality
may be less sensitive than the perfusion image. Two-dimensional echocardiography is sensitive for detection of localized disorders of contractility and for differentiation of previous myocardial infarction (Thomas, 1996).

Already in 1982, Braunwald and Kloner pointed out that the myocardium after a short-term ischemia showed a transitory delay in the recovery of cardiac function after establishment of coronary flow. This reaction of the myocardium to ischemia after reperfusion was defined as "stunned myocardium". Stunned myocardium or postischemic dysfunction is a mechanic systolic and/or diastolic dysfunction, which is maintained after reperfusion in spite of the absence of any irreversible damage. The main feature of this condition is complete reversibility of the disorder (Braunwald and Kloner, 1982).

Almost 70 years ago, Tennant and Wiggers observed that repeated recovery of coronary blood flow might cause arrhythmia. In experimental conditions it happened within a few seconds after reperfusion. In humans, reperfusion arrhythmias were most often accompanied by a primary PTCA* (Percutaneous Transluminal Coronary Angioplasty), intracoronary thrombolytic therapy and rarely during intravenous thrombolysis (Grech et al., 1995). Reperfusion arrhythmia might be a cause of sudden death in acute myocardial infarction. However, it was found that some patients, after successful coronary recanalization of the infarcted artery, show an idioventricular rhythm with potential serious hemodynamic effects within 1 min after balloon deflation during PTCA. Sinus rhythm was established after repeated inflation of the balloon and consequent interruption of the oxygenated blood supply, which indicated that the established reperfusion with consequent reoxygenation was a primary factor of arrhythmogenesis (Grech and Ramsdale, 1994; Rosenbaum et al. 1994).

The aim of our study was to investigate the time correlation between the establishment of reperfusion and the wall motions of the corresponding part of the left ventricle after successful recanalization of the infarction-related coronary artery. The second goal was to determine the appearance of reperfusion arrhythmia, their extent, form and the moment after the onset of reperfusion, when arrhythmia follows the establishment of the coronary flow.

MATERIAL AND METHODS

Fourteen dogs weighing 18±5kg were anesthetized by sodium pentobarbital intraperitoneally (30mg/kg of body weight) and artificially ventilated by a CEP ASEARLE respirator. We chose this anesthetic for its minimal arrhythmogenic effect, and smallest influence on the hemodynamics and extent of necrotic tissue area (Chakrabarty et al., 1991). The heart was exposed through a medial sternotomy and pericardectomy. For administration of contrast agent, a modified pigtail catheter was placed through the right carotid artery and positioned in the aorta just above the aortic valve. The left coronary artery was dissected free from surrounding tissues and an O DEXON PLUS ligature placed around it. These ties were used to occlude the artery and reperfusion was

* Primary PTCA-PTCA in acute myocardial infarction
established after 1, 2, 5, 10 and 15 min. The electrocardiogram was recorded continuously and elevation of the ST segment monitored. There were no significant hemodynamic problems during the intervention and all the dogs survived the experiment.

Echocardiography was performed with a commercially available 5MHz transducer (Toshiba SSH 60). The transducer was protected by a sterile plastic bag and for good resolution of the two-dimensional echo image, sterile gel was put in this plastic bag and warm saline solution poured over the exposed heart. Images of the left ventricle were obtained in a short axis cross-sectional view at the mid-papillary muscle level. This view enables demonstration of three different coronary perfusion beds: the left coronary descending, left circumflex and right coronary artery. The best quality of two-dimensional echocardiographic images was obtained in the perfusion area of the left coronary artery that was studied. The imaging plane depth and gain settings were optimized in the position of the best visualization of the contrast effect at the beginning of the study, and were not changed during the examination. All images before, during and after injections of contrast material were recorded on VHS videotape for later analysis.

We used an original contrast agent, AQ-DDT, produced in the laboratory of the Institute for Cardiovascular Diseases of the Clinical Center of Serbia in Belgrade (Arandelović et al., 2003). Each dog received a volume of contrast agent sufficient for good opacification of the left ventricular myocardium (between 1.0-2.5ml).

Regional left ventricular wall motion was described as normal, hypokinetic, akinetic and dyskinetic. Regional abnormalities of wall motion include diminished inward motion of a myocardial segment (hypokinesis), no inward movement of a myocardial segment (akinesis), and paradoxical systolic expansion of a regional myocardial segment-myocardial segment moving outward during systole (dyskinesis) (Hoffmann, 1996; Jae et al. 1999).

Ventricular rhythm disorders defined as reperfusion arrhythmias were: ventricular premature complexes (VPCs), ventricular tachycardia with interruptions (nonsustained VT-more or equal 3 and less than 20 VPCs), permanent ventricular tachycardia without interruption (sustained VT-more or equal 20 VPCs) and ventricular fibrillation (VF). VPCs are a manifestation of abnormal automaticity of a protected ventricular focus; because it is not penetrated by sinus impulses, it is not reset by them and the interectopic intervals remain relatively fixed. VPCs are recognized by wide (usually >0.14s), bizarre QRS complexes that are not preceded by P waves (Josephson et al. 1991). The occurrence of three or more consecutive premature ventricular complexes with a rate greater than 100/min is considered to be ventricular tachycardia (VT). If it ceases spontaneously, it is called nonsustained; if not, it is called sustained. VF is a highly disorganized rhythm with continuously varying QRS amplitude (<0.2mV), morphology (wide, bizarre QRS) and rate (150-500/min) (Balke et al. 1981; Josephson et al., 1991).

Establishment of perfusion was a necessary condition to qualify as reperfusion arrhythmia considering literature data stating that reperfusion arrhythmias do not always follow the establishment of blood flow (Grech and
Ramsdale, 1994; Grech et al., 1995). We analyzed the establishment of reperfusion, segmental wall motion and appearance of reperfusion arrhythmias.

RESULTS

Before the coronary occlusion, a myocardial echocardiographic contrast effect was clearly visible in all cases. Segmental wall motion disorders of the left ventricle were not registered. During the placement of the echocardiographic probe on the heart surface, a single VPCs appeared only in one case, but it was of a transitory character.

After coronary occlusion, we obtained the results shown in Table 1.

Table 1.

<table>
<thead>
<tr>
<th>Period of occlusion (min)</th>
<th>Disorders of left ventricular wall motion</th>
<th>Reperfusion arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without disorders</td>
<td>Hypokinesia</td>
</tr>
<tr>
<td></td>
<td>N=14</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Duration of the occlusion for 1min practically was accompanied neither by disorders of left ventricular wall motion (13/14), nor by ventricular rhythm disorders (13/14) after reperfusion was established.

Already after 2min of occlusion, the first segmental wall motions disorders appeared in the majority of the experimental animals (12/14), with the greatest frequency in the form of hypokinesia (10/12). The frequency of reperfusion arrhythmias was significantly lower (5/12), mostly as nonsustained VT (4/5). These disorders became more prominent in proportion to the duration of occlusion, in all cases with longer ischemia (5,10,15 minutes). Motion disorders were increased with the duration of occlusion; akinesia was registered in the greatest number of cases after 15 min of cessation of the flow. In relation to the onset of ventricular arrhythmias after reperfusion, the majority of experimental animals showed the presence of rhythm disorders; mainly in the form of VT (sustained/unsustained). The appearance of VF in all cases was successfully interrupted by DC shock.

The time of onset of the phenomena related to the ischemia-reperfusion process is given in Table 2.
Table 2.

<table>
<thead>
<tr>
<th>Period of occlusion (min)</th>
<th>Cessation of occlusion</th>
<th>Appearance of reperfusion arrhythmias (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Establishment of perfusion (min)</td>
<td>Establishment of the wall kinetic (min)</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>7.6</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>18.5</td>
</tr>
<tr>
<td>15</td>
<td>1.7</td>
<td>33.7</td>
</tr>
<tr>
<td></td>
<td>1.24±0.4</td>
<td>12.26±4.4</td>
</tr>
</tbody>
</table>

After the occlusion of the proximal part of the left coronary artery, the period for establishment of the blood flow was, on average, 1.24±0.4 min. and was manifested as restored reperfusion of the ischemic region. In cases where the establishment of the coronary flow was accompanied by reperfusion arrhythmias, these rhythm disorders developed on average, 6.44±2.3 min. after reperfusion; minimally after 2 min. of occlusion duration (1.5 min) and maximally after 15 min of interruption of the circulation (15.0 min).

In relation to the establishment of ischemic region kinetics, we observed that this positive effect of reperfusion recovered most slowly (12.26±4.4 min). The wall motion of the left ventricle was established fastest after the short term of occlusion (1.0 min), practically immediately after the establishment of blood flow. However, the longer the period of the cessation of blood flow, the longer the period of contractility recovery. The wall motions were not achieved until half an hour after reperfusion (33.7 min) depending on the duration of occlusion (15 min).

DISCUSSION

Early coronary reperfusion as a treatment for acute myocardial infarction decreases the size of the infarcted area, improves the function of the left ventricle, and also the time of survival. However, in some way paradoxically, reperfusion, i.e. establishment of a good coronary flow, may cause myocardial damage – reperfusion injury (Jurkovičová and Cagáň, 1993). Four basic forms of reperfusion injury were identified: 1. Lethal reperfusion damage (death of cardiac myocytes caused directly by reperfusion); 2. Vascular reperfusion damage, experimentally proven but uncertain in humans. It involves progressive damage of the vascular network during the reperfusion and is manifested by extension of ischemic region; 3. Stunned myocardium. This is postischemic myocardial dysfunction of living cardiac myocytes, and probably represents a form of “functional reperfusion damage”, i.e. a delay of functional recovery. It is characterized by slow, gradual
recovery of contractile function after reperfusion. This recovery of the functional capacity is complete but requires hours or days (Braunwald and Kloner, 1982). Experimental studies confirmed that stunned myocardium is a reversible condition, which may be corrected by inotropic agents. The question is whether this reversibility is the consequence of an inotropic action or a mechanical-circulatory support, because of the potential danger of an overdose of inotropic drugs, which increase myocardial oxygen consumption, and are arrhythmogenic (Hoffmann, 1996); 4. Reperfusion arrhythmias as the fourth form of reperfusion injury, will be discussed later below.

Left ventricle wall motion

Reperfusion without myocardial stunning may result in immediate and complete recovery of myocardial contractile function. However, this can be seen only after a very short ischemic episode (1-2 min of coronary occlusion), while longer episodes of ischemia (>2min) are accompanied by a certain degree of myocardial stunning (Braunwald and Kloner, 1982). Our study confirmed this, because after a short time of occlusion (1 min) disorders of contractile function practically were not registered and after occlusion of 2 min the consequent kinetic disorders recovered relatively fast.

It was shown that the severity and duration of previous ischemia (Braunwald and Kloner, 1982) primarily determined the severity of postischemic dysfunction. This was confirmed by our study as akinesia was found in the greatest number of cases (11/14), after 15 min of occlusion. Earlier studies showed different times for functional recovery of left ventricle regional wall motion after the cessation of occlusion (Bolli et al., 1986; Conorev et al., 1990; Grech and Ramsdale, 1994; Russell et al., 1982). The majority of motion disorders are present for a few minutes allowing their detection, although regional kinetic disorders may sometimes last more than 30 min after an established reperfusion (Thomas, 1996). In our study the establishment of wall motion was achieved after 12.26 ± 4.4 min, so we did not have cases of prolonged recovery. However, after 15 min of occlusion and ischemia, segmental wall motions were established 30-min later, which corresponds to the literature data (Galinanes et al. 1987; Nearing et al., 1994; Rosenbaum et al., 1994).

In the greatest number of cases regional myocardial dysfunction is visible on the echocardiograph before one of the most common manifestations of ischemia, depression of the ST segment (Hoffmann, 1996; Jae et al., 1999). Experimental studies showed that segmental wall motion dissynergy develops very soon after interruption of the coronary flow. Therefore, echocardiography is a sensitive diagnostic method, which may define segmental wall motion disturbances very early, especially in early ischemia (Jae et al., 1999).

Our results also showed that in nearly all the cases studied segmental wall motion disorders were found 2 min after the duration of the occlusion (12/14 cases).
Reperfusion arrhythmias

Reperfusion arrhythmias are the fourth form of reperfusion injury. An early (within 6 hours after the start of thrombolysis), frequent (>30 episodes/hour) and repetitive (occurring during >3 consecutive hours) accelerated idioventricular rhythm (AIVR) is considered as a typical reperfusion arrhythmia. AIVR with such characteristics has high specificity and positive predictive accuracy but relative low sensitivity as a predictor of reperfusion (Jurkovicová and Cagáň, 1993). The following arrhythmias are also regarded as markers of reperfusion: frequent VPCs (>twofold increase in frequency within 90 minutes after the start of thrombolysis), a significant increase of episodes in niVT, sinus bradycardia and high-degree atrioventricular blocks. There is no definite evidence, as to whether sVT and especially VF can be caused by reperfusion (Jurkovicová and Cagáň, 1993).

Another author emphasized that reperfusion arrhythmias just include ventricular tachycardia and fibrillations, which develop within a few seconds to few minutes after established reperfusion, and after short (5-15 min) episodes of myocardial ischemia (Kloner, 1993). Real reperfusion arrhythmias develop only in a small number of cases which receive thrombolytic therapy after acute myocardial infarction and are not a sensitive indicator of successful reperfusion (Kloner, 1993). Moreover, our results demonstrate that the appearance of reperfusion arrhythmias does not follow each successful reperfusion. These disorders of rhythm can be a significant noninvasive indicator of successful coronary recanalization of the infarction-related coronary artery, but also can be a sign of reperfusion damage, which can limit the favorable effects of reperfusion. The undesired effect is related to the appearance of VF, which does not often occur (4/14 in our study), but represents a serious disorder of rhythm.

Reperfusion ventricular tachyarrhythmias may appear in their early form at 5-6 min, and in later form within 18-20 min after the established reperfusion, which is significant in understanding severe rhythm disorders in acute myocardial ischemia and infarction (Balke et al., 1981). Early ventricular arrhythmias are related to fast changes in regional myocardial flow and in electrophysiological changes; local spatial variability of flow in the central ischemic region may be a precondition for inadequate distribution of conductibility leading to reentry, excitation and appearance of early ventricular arrhythmias (Bolli et al., 1986; Russell et al., 1982).

It was found that during the first day after reperfusion, nonsustained VT and single VPCs were established most frequently. Their number and frequency decreased by the end of the first week (Jurkovičová and Cagáň, 1993). According to our results, ventricular rhythm disorders after reperfusion appeared faster than was reported in the literature, especially in short term occlusions (1.5-2.3 min.), while after 15 minutes of occlusion reperfusion was followed by arrhythmias appearing 15min later.

Arrhythmias may occur also in the late phase of reperfusion; more than 3 days after an episode of between 15 min and 4h of coronary occlusion. Transient occlusion up to 5 min does not cause late reperfusion arrhythmia, but a special arrhythmogenic effect in the late phase may follow occlusions of 4h and gradually
decrease after a period of 3 days (Lo et al. 1989). In our experiment late reperfusion arrhythmias were not studied.

The duration of a previous ischemia is a second important factor of sensitivity to arrhythmia after reperfusion. The frequency of VF in humans was higher if ischemia was shorter (67%-20-30 min ischemia: 22% after 60 min ischemia), which indicates that if thrombolytic therapy treatment is applied as soon as possible, a higher frequency of reperfusion arrhythmia may be expected (Dezhi Xing and Martins, 2001; Lo et al, 1989). In our experimental study a small number of VF cases (4/14) was registered, so, there were not enough elements for analysis. According to our results we can give the following main conclusions: 1. Left ventricle wall motion abnormalities are, in most cases, a sign of coronary circulation damage. 2. Wall motion disorders appear as a first manifestation of ischemia but they recover slowest after reperfusion is established. 3. Reperfusion arrhythmias do not always follow reperfusion, but when they do, they usually manifest in nVT form. 4. If present, reperfusion arrhythmias appear before left ventricle wall motion is established.

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UPOREDA STUDIJA POKRETA ZIDOVA LEVE KOMORE I REPERFUZIONIH ARITMIJA KAO ZNAKOVA USPESNE KORONARNE REKANALIZACIJE

ARANĐELOVIĆ ALEKSANDRA, MALOBABIĆ S., NIKOLIĆ VALENTINA i ŻUNIĆ SNEŽANA

SADRŽAJ

Posle kontrolisane ishemije srca vršeno je poređenje regionalne disinerije miokarda i aritmije kao posledica reperfuzije. Pri tome je analizirano uspostavljanje reperfuzije, uspostavljanje pokreta zida leve komore (ehokardiografijskom) i pojava reperfuzionih aritmija. U aortu četnaest pasa ubrizgavan je ehokardiografski kontrast (AQ-DDT), i istraživana perfuziona oblast miokarda je prikazivana dvodimenzionalnom ehokardiografiom. Okluzija je izazivana podezivanjem leve koronarne arterije, a potom je reperfuzija uspostavljana posle 1, 2, 5, 10 i 15 min. Regionalni pokreti ventrikularnog zida su određivani kao normalni, hipokinetički, akinetički i diskinetički. Poremećaji ventrikularnog ritma definisani kao reperfuzione aritmije su: ventrikularni prematurni kompleksi, ventrikularna tahikardija sa prekidima, permanentna ventrikularna tahikardija bez prekida i ventrikularne fibrilacije. Pre koronarne okluzije efekti ehokardiografskog kontrasta su bili jasno vidljivi u svim slučajevima. Posle okluzije proksimalnog dela leve koronarne arterije, period uspostavljanja krvotoka bio je u proseseu, 1,24 ± 0,4 min. U slučajevima u kojima je uspostavljanje koronarnog krvotoka bilo praćeno reperfuzionim aritmijama, ovi
poremećaji ritma su se razvijali u proseku 6,44±2,3 min. posle reperfuzije; minimalno posle 2 min. (1,5 min) i maksimalno posle 15 min (kod trajanja okluzije15.0 min). Pozitivan efekt reperfuzije, uspostavljanje pokreta ishemičnog regiona, pokazivao je najsporiji oporavak (12,26 ± 4,4 min). Najbrže su uspostavljani pokreti zida leve komore posle kratkotrajne okluzije (1,0 min), praktično neposredno po uspostavljanju krvotoka. Međutim, što je duži bio period prekida krvotoka, duži je bio i period oporavka kontraktilnosti, jer su se pokreti zida javili pola sata po uspostavljanju reperfuzije (33,7 min), ako je period okluzije bio duži (15 min). Autori zaključuju da se abnormalnosti pokreta zida leve komore najčešće pojavljuju kao znak oštećene koronarne cirkulacije; da se poremećaji pokreta zida pojavljuju kao prve manifestacije ishemije, ali se najsporije oporavljaju po uspostavljanju reperfuzije; da se reperfuzione aritmije ne pojavljuju uvek posle reperfuzije i da ako su prisutne, reperfuzione aritmije nastaju pre uspostavljanja pokreta zida komore.