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AN EXPERIMENTAL INTRAOPERATIVE QUANTITATIVE ECHOCARDIOGRAPHIC STUDY OF MYOCARDIAL PERFUSION IN DOGS

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Myocardial contrast echocardiography is a valuable technique for demonstration and delineation of regions of myocardial underperfusion secondary to coronary occlusion and/or significant coronary stenosis. Various contrast materials have been used. The aim of this study was to determine whether myocardial contrast echocardiography by the original contrast agent AQ-DDT (albumin based), produced in the Institute for Cardiovascular Diseases, Clinical Center of Serbia in Belgrade can be used in the detection and quantification of regions of myocardial perfusion defects.

In 14 adult open chest dogs the perfusion defect was produced by selective coronary ligations (30 seconds) and was observed with epicardial contrast two-dimensional echocardiography. For administration of contrast a modified pigtail catheter was positioned in the aorta just above the aortic valves. In this way the perfusion regions of the left main and right coronary artery were included. The left anterior descending and left circumflex artery could not be selectively injected with contrast agent and their individual perfusion areas were not clearly demonstrated.

In all cases contrast echocardiography images of the left ventricle were obtained in a short-axis cross-sectional view at the mid-papillary muscle level. Forty-two injections of AQ-DDT for perfusion analysis were done, and were recorded on a VHS recorder. Quantification of the quality in demonstrating myocardial perfusion was scored as good, poor or without visual echocardiographic effect, by an investigator experienced in echocardiography, immediately and one month later. There was 100% agreement in the scoring. Our results indicated that agent AQ-DDT produces a good contrast effect (echocardiography visualization) in dogs and has the potential to demonstrate regional perfusion defects of the myocardium. Its potential role in human medicine, for diagnosis and evaluation of the results of interventional therapy, especially during aortocoronary bypass graft surgery, should be evaluated.

Key words: echocardiography, dogs, coronary occlusion, myocardial perfusion, contrast medium

INTRODUCTION

Myocardial contrast echocardiography has been a major research objective in cardiovascular ultrasound studies for almost two decades. The assessment of myocardial perfusion by ultrasound – enhancing agents has been tested in different experimental and clinical settings, potentially adding a new dimension to echocardiography (Maurer, 2000). Contrast echocardiography has contributed greatly to the understanding and in vivo identification of cardiac structures and physiological phenomena. The first contrast substances used were indocyanine green solution, saline, dextrose in water and the patient's blood. Progress in assessing myocardial perfusion by contrast echocardiography was related to the measurement of coronary flow reserve and to the evaluation of new ultrasound contrast agents (Schneider, 2000). Therefore, myocardial contrast echocardiography has undergone extensive validation in experimental animals as a method for the in vivo detection and quantification of underperfused myocardium (Armstrong *et al.*, 1982; Armstrong *et al.*, 1983; Gertjan, *et al.*, 2000; Kemper *et al.*, 1983; Klipcera *et al.*, 1982).

In the 1970s and early 1980s contrast echocardiography played an important role in the validation of anatomic structures. A few years later a number of studies approved the use of contrast echo for delineating regional perfusion deficits (Kaul *et al.*, 1984; Maurer, 2000). Myocardial contrast echocardiography performed with sonicated diatrizoate meglumine (Renographin 76) or sonicated human albumin (Albunex®) can delineate areas of underperfused myocardium after coronary occlusion and in the presence of critical coronary artery stenosis (>75%).

The aim of this study was to determine whether a new contrast agent AQ-DDT, produced in the laboratory of the Institute for Cardiovascular Diseases of the Clinical Center of Serbia (Belgrade) and used during intraoperative echocardiography, could be valuable in the detection and quantification of regions of myocardial underperfusion resulting from coronary occlusion.

MATERIAL AND METHODS

Fourteen dogs weighing 18±5kg were anesthetized with sodium pentobarbital given intraperitoneally (30 mg/kg of body weight) and artificially ventilated by a CEP ASEARLE respirator. The heart was exposed through a medial sternotomy and pericardiectomy. For administration of contrast agent a modified pigtail catheter was placed through the right carotid artery and positioned in the proximal aorta just above the aortic valve. The left main (LM) and right coronary artery (RCA) were dissected free from surrounding tissues and O DEXON PLUS ties were placed around them. These ties were used to occlude the selected artery (for a period of 30 seconds); LM in seven dogs and RCA in the other seven. Continuous recordings were made on the electrocardiogram and, after the appearance of an elevated ST segment, occlusion of the artery was immediately stopped. There were no significant hemodynamic problems during the interventions. Only one

dog had ventricular fibrillation during ligation of the RCA but it was successfully defibrillated.

Echocardiographic studies were made using a commercially available 5MHz transducer (Toshiba SSH 60). The transducer was protected with a sterile plastic bag and, for good resolution of the two-dimensional echo picture, sterile gel was put in this plastic bag and warm saline solution was 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 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 a VHS tape for later analysis. We used on original contrast agent AQ-DDT (aqueous solution of dense albumin) produced in the laboratory of the Institute for Cardiovascular Diseases of the Clinical Center of Serbia in Belgrade. Each dog received 3 injections of AQ-DDT and a volume of contrast agent sufficient for good opacification of the left ventricular myocardium, which was 1.0-2.5ml. Forty-two injections for perfusion analysis were made and scored by an investigator experienced in echocardiography, immediately and one month later. There was 100% agreement between these two scores.

The effects of contrast echocardiography were quantified as a good, poor and absent visualization. Good effects were defined as a clear demonstration of diffuse contrast flow in all segments of the left ventricle supplied by the investigated artery. The cases with partial (incomplete) demonstration of contrast distribution were scored as poor effects. Absent visualization was defined as complete absence of visualization of contrast.

RESULTS

The appearance of the myocardium before administration of contrast medium is shown in Figure 1.

In dogs with normal coronary arteries (before occlusion), the entire myocardium was demonstrated as uniformly and simultaneously opacificated after injection of contrast agent. Proximal vascular beds of the coronary arteries in the first phase of contrast injection are shown in Figure 1A.

In dogs with coronary artery occlusion contrast echocardiography demonstrated persistent dark areas (Fig. 1B), where contrast agent had been present before occlusion (Fig. 1A).

The best quality images were obtained in the left coronary perfusion bed (Fig. 2). This large vascular bed was completely demonstrated by the AQ-DDT contrast agent.

Figure 1. Contrast echocardiography in dogs. Short -axis view of the left ventricle at the mid-papillary muscle level. Visualization of the myocardium before administration of contrast agent

Figure 1A. Contrast echocardiography in dogs. Short -axis view of the left ventricle at the mid-papillary muscle level. Homogenous opacification of the myocardium (outlined with white line) after administration of contrast agent in to the proximal aorta

Figure 1B. Contrast echocardiography in dogs. Short -axis view of the left ventricle at the mid-papillary muscle level. Loss of contrast effect in the perfusion area (outlined with white line) of RCA after its occlusion

Figure 2: Contrast echocardiography in dogs. Short -axis view of the left ventricle at the mid-papillary muscle level. An intensive contrast effect in the perfusion area of the left coronary artery

Quantification of effects of myocardial contrast echocardiography before coronary occlusion is presented in Figure 3.

It is obvious that in nearly 80% (78.6%) of the dogs without coronary occlusion the effects of the contrast agent we are good. Complete failure (absent visualization) was present in only 7.1% of these dogs.

Figure 3. Contrast effect before ligation of the coronary artery (N=42 injections)

Scores of the effects of contrast echocardiography after coronary occlusion are presented in Figure 4.

Figure 4. Contrast effect after ligation of the coronary artery (N=33 injections). These effects were scored in those regions of the myocardium where the vascular beds were not occluded, i.e. with remaining good perfusion

It is interesting that in these cases the effects of contrast agent in the remaining regions were increased, suggesting the existence of some compensatory mechanism to elevate blood flow in intact myocardial regions. Underperfused regions obviously were without visualization.

DISCUSSION

Myocardial contrast echocardiography offers the potential to provide many types of information about myocardial perfusion (Schneider, 2000). After myocardial infarction, it is a way of assessing infarct size and areas at risk. Also, it can help in studies of the no-reflow phenomenon, coronary flow reserve, the presence, extent and adequacy of the collateral circulation and of myocardial viability (Gertjan, *et al.*, 2000; Kamp *et al.*, 1989; Lindner *et al.*, 2000; Maurer, 2000; Schneider, 2000).

When micro bubbles of contrast agent are administered at the site of cardioplegia delivery, evaluation of regional differences in myocardial contrast effect can indicate the adequacy of intraoperative myocardial protection. The purpose is to minimize perioperative myocardial damage, to achieve adequacy of revascularization and to differentiate stunned from ischemic postoperative myocardial dysfunction (Aronson, 1993). (Stunned myocardium is dysfunction with preserved perfusion and ischemic myocardium implies decreased function and perfusion). Hence, myocardial contrast echocardiography offers a unique, readily implementable opportunity to optimize coronary artery by pass grafting procedures (Villaneuva *et al.*, 1992a).

The present study demonstrates the high quality of AQ-DDT as a contrast agent in the estimation of the size of areas of underperfused myocardium in the presence of complete coronary occlusion with an accuracy similar to those obtained by other different contrast agents (Almeida *et al.*, 2001; Tiemann *et al.* 1999; Haluska, *et al.* 1999; Lindner *et al.*, 2000; Jayaweera, Sklenar and Kaul, 1994; Kaul *et al.*, 1984; Villanueva *et al.*, 1992a; 1992b; Wei *et al.*, 2000; Tiemann, *et al.*, 1999; Wei, 2001; Porter, Kricsfeld and Armbuster, 1997; Porter *et al.*, 1999). Also, our results indicate that myocardial perfusion with AQ-DDT contrast agent correlates well with the actual coronary anatomy in the dog.

The best quality of two-dimensional echo images was obtained in assessing the left coronary perfusion bed, which corresponds to the results of previous investigations. The sensitivity of contrast echocardiography in the detection of significant coronary stenosis in the septal or left anterior descendent region was shown to be 96% compared to 100% for the anterolateral or circumflex region and only 58% for the inferior or right coronary area (Cheirif *et al.*, 1989; Galiuto and Iliceto, 1998; Goldman and Mindich, 1984; Ito *et al.*, 1992; Jayaweera and Kaul, 1993). It is harder to assess the right coronary artery system, since the particular echo view at the short axis mid-papillary muscle level may give a false echo contrast image of the posterior wall of the left ventricle. This problem of improvement of the effect of contrast visualization may be solved by direct administration of contrast into the coronary artery.

Several factors may influence the visualization of contrast agent during echocardiography: the nature of the agent, the way of its preparation, its temperature and rate of perfusion (Gertjan *et al.*, 2000; Schneider, 2000; Tei *et al.*, 1983). Each of these factors might influence the quality of echo image in those of our cases with a poor effect of myocardial perfusion.

Our experimental results in dogs indicate that an albumin based original contrast agent (AQ-DDT) produces a good two-dimensional contrast echo image both for demonstration and good delineation of regional perfusion defects of the myocardium in dogs. We are sure that further clinical trials will confirm our conclusions about the suitability of AQ-DDT contrast agent in diagnosis and evaluation of the results of interventional therapy (coronary artery bypass graft or transluminal coronary angioplasty).

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EXPERIMENTALNA INTRAOPERATIVNA KVANTITATIVNA EHOKARDIOGRAFSKA STUDIJA MIOKARDIJALNE PERFUZIJE U PASA

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SADRŽAJ

Kontrastna ehokardiografija miokarda je korisna tehnika prikazivanja i ograničavanja regiona slabije perfuzije miokarda izazvane okluzijom ili stenozom koronarnih arterija. U ovoj tehnici se koriste različiti kontrastni materijali. Cilj našeg istraživanja je bio da se utvrdi da li se kontrastna ehokardiografija originalnim kontrastnim sredstvom AQ-DDT proizvedenim u laboratoriji Instituta za kardiovaskularne bolesti Kliničkog centra Srbije može koristiti u određivanju i kvantifikaciji onih regiona sa deficitom u perfuziji miokarda.

Defekt u perfuziji miokarda izazivan je na 14 pasa selektivnim podvezivanjem koronarnih arterija tokom 30 sekundi. Istraživanje je vršeno epikardijalnom kontrastnom dvodimenzionalnom ehokardiografijom. Kontrast je ubacivan u aortu neposredno iznad zalistaka modifikovanim "pigtail" kateterom. Na ovaj način smo obuhvatili perfuzione oblasti kako leve, tako i desne koronarne arterije. Oblasti prednje descendentne i leve cirkumfleksne arterije nisu mogle biti jasno prikazane.

U svim slučajevima kontrastna ehokardiografija miokarda leve komore vršena je nivou ravni koja prolazi kroz sredinu papilarnih mišića. Ukupno su izvršene 42 injekcije AQ-DDT koje su u cilju analize perfuzije snimljene na video rikorder. Efekti prikazivanja miokardne perfuzije ocenjivani su od strane iskusnog ehokardiografiste kao dobra, loša i odsutna vizualizacija, neposredno tokom studije i ponovo mesec dana kasnije. Svi naši rezultati ukazuju da kontrastno sredstvo AQ-DDT ima dobar kontrastni efekt (ehokardiografsku vizualizaciju) u pasa i da ima potencijal za prikazivanje regionalnih defekata u perfuziji miokarda.