Intra-operative contrast echocardiography in coronary artery disease

P. VOCI
Department of Cardiac Surgery, "La Sapienza" University of Rome, Italy

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Intra-operative echocardiography is becoming a reference standard for the evaluation of the results of cardiac surgery. Myocardial contrast echocardiography has been recently introduced to study regional myocardial blood flow and cardioplegia distribution in patients undergoing coronary artery surgery. It can be used in three different stages: before cardiopulmonary bypass, to identify the most hypoperfused myocardial segments; during cardioplegic arrest, to check the distribution in patients undergoing coronary artery surgery. It can be used in three different stages: before cardiopulmonary bypass, to identify the most hypoperfused myocardial segments; during cardioplegic arrest, to check the adequacy of myocardial protection; postoperatively, to assess graft patency. The priority in revascularization can be assigned according to the regional perfusion pattern, which depends not only on coronary artery narrowing, but also on the extent of collateral circulation. The distribution of cardioplegia to the myocardium can be monitored in real time with clear identification of poorly protected myocardial segments. The injection in the graft after weaning from cardiopulmonary bypass allows assessment of graft patency and measurement of the 'area at risk' for graft occlusion. In conclusion, the information obtained in the operating theatre by myocardial contrast echocardiography is original and promises to have a significant impact on surgical strategy. Implementation of the ultrasonic equipment to obtain quantitative on-line data on myocardial blood flow is desirable.

Introduction

Intra-operative echocardiography was introduced in 1972 by Johnson et al. to evaluate the results of mitral valve surgery and is now an established technique to define cardiac anatomy during open chest surgery. In the last few years Doppler echocardiography has been established as a reference standard for the intra-operative assessment of left ventricular function, intracardiac shunts and valvarular regurgitations. Myocardial contrast echocardiography has been recently introduced in the surgical arena to explore a new and exciting feature of cardiac pathophysiology: regional myocardial blood flow. In this article, the potential intra-operative applications of this new technique will be discussed, with particular reference to coronary artery bypass grafting.

The agent

Ultrasonic energy propagated through a medium may be treated as a wave form similar to that of light energy. Thus, understanding the laws of physics governing ultrasonic energy scattering is important for the study of quantitation in the field of contrast echocardiography. Accordingly, the magnitude of the reflected and refracted sound energy is influenced by the acoustic impedance or mismatch between two contiguous media. The acoustic interface between air and blood is characterized by a marked impedance. Consequently, the most reflective echo contrast agents are made of air bubbles.

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Correspondence. Dott Paolo Voci, Via San Giovanni Eudes, 27, 00163 Rome, Italy

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carrier solution, small, uniform (4 ± 1 micron in diameter) and stable microbubbles are generated. These microbubbles are smaller than red blood cells, they are non-diffusible to the extravascular space and they flow unimpeded through the capillaries. In addition, albumin microbubbles are isosmotic and do not alter the flow pattern.

When bubble dimensions are maintained constant, the reflected signal is proportional, within certain limits, to concentration. The application of the mathematical formulae derived from the indicator-dilution theory to this new imaging modality allows the study of blood flow and volume in organs accessible to ultrasound.

Safety

The safety issue in contrast echocardiography was extensively discussed in a large survey of the American Society of Echocardiography. Only minor side effects were encountered in a series of 51189 patients undergoing intravenous injection of hand-agitated agents, with an overall estimated risk of complications of 0.062%.

Sonicated agents contain smaller and more uniform microbubbles, thus, these tracers should be considered safe for intravascular injections, and no significant side effects were reported after intracoronary or intra-aortic injections of these agents. Transient wall motion abnormalities were reported to have occasionally occurred with some of the radiopaque compounds. However, these changes were not clearly demonstrated to be the direct effect of the microbubbles but were due, in part, to the hyperosmolar content of the carrier solution.

However, the production of albumin microbubbles should be performed in accordance with strict guidelines. The high-energy ultrasonic waves employed in sonication start a cascade phenomenon, which rapidly increases the solution temperature. Excessive denaturation of albumin, which is a thermolabile protein, should be avoided to prevent focal or diffuse coagulation. Accurate selection of the agent in vitro is very important in order to eliminate any microbubbles that may generate during the procedure. Large albumin bubbles should be discarded because they are fairly stable in vivo, pressure-resistant and may induce significant microembolization.

Intra-operative applications

Myocardial contrast echocardiography can be used in three different stages during coronary surgery: pre-operatively, to identify the most hypoperfused myocardial segments; during cardioplegic arrest, to check the adequacy of myocardial protection; postoperatively, to assess graft patency. Each of these points is crucial in coronary surgery and leads to a common important goal: the reduction of peri-operative myocardial infarction.

Coronary surgery may improve left ventricular function, but if peri-operative myocardial infarction occurs, the left ventricular function may be significantly compromised. Preventing peri-operative myocardial infarction also leads to a reduction in morbidity and mortality associated with coronary surgery.

Priority in revascularization

One way of reducing the risk of peri-operative myocardial infarction is to first bypass the most stenotic major coronary artery. This decision is usually based on semiquantitative and subjective visual interpretation of pre-operative coronary angiograms. However, the morphological aspect of a coronary stenosis is poorly correlated with coronary and myocardial blood flow. In addition, sequential coronary stenoses and collateral circulation are further confounding factors in the evaluation of the physiological impact of coronary artery disease in the individual patient. Moreover, myocardial blood flow is influenced not only by percent coronary narrowing, but also by the status of the microcirculation, left ventricular hypertrophy and loading conditions.

Myocardial contrast echocardiography permits the direct visualization or imaging of blood flow and tissue volume status at the microcirculatory level. Any alteration in blood flow, regardless of its cause, should thus be detected. The most relevant clinical parameters provided by this technique are the extent of the myocardial area subserved by each coronary artery, and the relative degree of segmental hypoperfusion. These two parameters are potentially useful in assigning the priority in revascularization to the myocardial area at greatest risk of peri-operative injury.

Cardioplegia distribution

Complete myocardial protection is very important to reduce anoxic myocardial damage during coronary surgery. Although different techniques have been clinically used, a reliable and easy method for monitoring cardioplegia distribution is still lacking. The only available methods so far (temperature probes, vital dyes and ECG) are only indirect and rough estimators of myocardial protection. In addition, important cardiac structures, such as the interventricular septum, cannot be explored by these techniques.

Myocardial contrast echocardiography is the only imaging method allowing the on-line visualization of cardioplegia distribution. In 1984 Goldman and Mindich found that, when cardioplegia is delivered as a turbulent flow, it generates air bubbles, leading to a 'spontaneous' myocardial echocontrast effect. These authors showed that the pattern of myocardial contrast was well correlated with perfusion. However, as bubble formation at the tip of the catheter was inconstant, this study was not easily reproducible. Most importantly, bubbles produced in this way are trapped in the microcirculation and cannot be used as true indicators of flow. The development of standardized echocontrast agents with controlled bubble concentration and dimensions overcame these limitations.

Sonicated albumin is the most appropriate agent to study cardioplegia distribution, because of its favourable flow characteristics, and because it can be stored sterile in...
a vial and used at room temperature. Other sonicated agents, such as radiopaque compounds, have a short half-life (1 to 3 min), and should be injected early after sonication. Although the temperature of the injected bolus may drop from 65 °C to 40-45 °C, this temperature is still too high for intra-operative use. Any increase in the temperature of the cardioplegic solution is to be avoided, because it may hamper myocardial protection.

The echocontrast agent is injected as a bolus through the cross-clamped aortic root, along with antegrade cardioplegia. The left ventricle is imaged by epicardial or transoesophageal echocardiography in the short-axis view at mid-papillary muscle level. In this projection, the territories of all three coronary arteries and of their major branches are simultaneously imaged. With retrograde cardioplegia the echocontrast agent may be injected either in the coronary sinus or in the right atrium, depending on individual cannulation technique.

The distribution territories for antegrade and retrograde cardioplegia are significantly different in patients with three-vessel disease. The retrograde perfusion route provides a more thorough or complete perfusion pattern when compared to the antegrade infusion pattern. These findings are not surprising considering that a critical coronary artery stenosis impedes antegrade cardioplegia flow, while retrograde flow is relatively unaffected. Figure 1 shows the left coronary angiography of a patient who underwent intra-operative myocardial contrast echocardiography. The left coronary artery was dominant. There was a total occlusion of the left anterior descending coronary artery distal to the first diagonal branch and a 90% stenosis of the distal circumflex coronary artery (Fig. 1(a)). Figure 1(b) shows the left ventricular short axis view of the same patient during cardioplegic arrest before and after (Fig. 1(c)) injection of 2 cc of sonicated albumin in the cross-clamped aortic root. The echo contrast agent opacifies only the antero-lateral wall, whereas a clear-cut perfusion defect outlines the interventricular septum and the posterolateral wall. An example of retrograde cardioplegia distribution is shown in Fig. 2. In this case, 4 cc of sonicated albumin were injected in the right atrium, resulting in a uniform myocardial distribution of the agent.

Cardioplegia administration may be modified by various non-coronary causes, such as the presence of a patent foramen ovale or aortic incompetence. In these conditions, the flow may be shunted from the coronary bed, resulting in impaired myocardial protection. This cardioplegia 'steal' can be easily detected by contrast echocardiography. During antegrade cardioplegia, the aortic cross-clamping may inadvertently cause aortic valve insufficiency. The solution regurgitates in the left ventricular cavity and is aspirated by left ventricular venting. Besides hampering myocardial protection, aortic regurgitation may cause left ventricular dilatation as well, a recognized untoward effect during heart surgery. Figure 3 shows a clear example of cardioplegia regurgitation in a patient with an otherwise normal aortic valve: the contrast, along with cardioplegia, fills the entire left ventricular cavity.

Right atrial cardioplegia may be impaired by two anatomical and functional conditions. The most important one is the presence of a patent foramen ovale, which
may drain an uncontrollable amount of the injected solution to the left atrium and ventricle. We observed this phenomenon in approximately 20% of our patients who underwent right atrial cardioplegia. A last, although less significant, shunt may occur between the thebesian veins and the atrial and ventricular cavities.

Contrast echocardiography may also be of help during aortic valve replacement. Myocardial protection is very important in patients with aortic valve disease as the hypertrophied and/or dilated left ventricle is particularly vulnerable to subendocardial ischaemia. Preservation of left ventricular function is in fact one major determinant of postoperative prognosis in these patients. During aortic valve surgery cardioplegia is administered by selective coronary cannulation. In the presence of a short left main coronary artery, either the left anterior descending or the circumflex coronary arteries may be inadvertently cannulated. In this situation, a large myocardial area is not protected. The intracoronary injection of 0.5 cc of sonicated albumin allows immediate identification of the perfused territories and eliminates the possibility of an inadvertent superselective coronary cannulation.

GRAFT PATENCY

When coronary surgery is completed, two urgent questions arise: the first is related to cardiac performance, and the second concerns graft patency. Evaluation of left ventricular wall motion and systolic wall thickening paves the way to the solution of the first problem. The second can be answered only using echo contrast agents.

There are two methods to check graft patency by contrast echocardiography. With the first one the agent is injected through the proximal end of the graft, as soon as distal anastomosis is completed (no blood flow in the graft); with the second one, the graft is injected as soon as proximal anastomosis is completed. The first method allows identification of the myocardial area reperfused by the injected vessel, although it cannot provide any information on graft flow. Two main reasons account for this limitation: first, the injection is performed during extracorporeal circulation, that is a non-physiological condition; second, the contrast bolus is very small (0.2-0.3 cc) and needs to be flashed by a second syringe. This involves an increasing variability related to velocity of injection.
The most physiological way to study graft patency and to calculate its flow is to inject the agent in the functioning graft after weaning from cardiopulmonary bypass. In a series of 12 consecutive patients with three-vessel disease we studied 19 saphenous vein grafts. The echocontrast agent (sonicated 5% human albumin) was prepared under sterile conditions one hour prior to surgery and stored in an insulin syringe at room temperature. The left ventricle was imaged in the transgastric short-axis view at mid-papillary muscle level. The injection of 0.3 cc resulted in an adequate myocardial opacification in 18 out of 19 grafts, and showed in real time (Figs. 4 and 5) the patency of the injected vessel. The myocardial contrast washout ranged from three to eight cardiac cycles, corresponding to the expected physiological transit time in normal coronary circulation.

This technique appeared to be safe: no additional wall motion abnormalities developed after each contrast injection and no side effects ascribable to the procedure were observed. Analysis of postoperative systolic function confirmed the effectiveness of revascularization, with percent systolic wall thickening increasing significantly after surgery in the opacified myocardial segments (from 12.6 ± 3.9 to 23.2 ± 4.6%; P < 0.05). Only one graft injection did not produce any myocardial opacification. In this patient the anastomosis was sutured on a 1 mm obtuse marginal branch and exhibited a very poor runoff. A small peri-operative myocardial infarction developed in the lateral wall.

Although these semiquantitative and morphological data convey important information in the surgical field, in contrast echocardiography the most ambitious goal is the quantitative assessment of regional blood flow. This can be accomplished by applying the mathematical formulae derived from the dye-dilution theory. Quantitative contrast echocardiography requires the digitalization of the echo contrast images and computer processing of the digital data. The variations in contrast (pixel) intensity with time are measured on a 64 gray-level scale. From the time-intensity plot, a gamma variate function is extrapolated. This function reflects the myocardial washout of the agent. Two important parameters for the application of the mathematical theory, the area under the curve and mean transit time, area derived.

Preliminary experimental studies demonstrate the feasibility of contrast ultrasonography for the in-vitro and...
Nevertheless, there are still many unresolved problems, which need to be addressed before transferring the experimental model for the quantitation of regional blood flow to human studies. The most important are the standardization of the injection technique and the in vivo stability of the agent which is not yet ideal.

Conclusions

Intra-operative myocardial contrast echocardiography opens a new and exciting chapter in cardiac pathophysiology. The information on blood flow provided by this technique are original and cannot be obtained by any other method. As intra-operative echocardiographic monitoring is becoming an accepted standard, and the echocardiographer is now part of the routine personnel in the operating room the additional costs of contrast studies are negligible. However, an implementation of the ultrasonic equipment to obtain on-line data on myocardial blood flow is desirable. The in vivo stability of the agent should be improved as well. A better understanding of cardiac pathophysiology in conjunction with an improved patient care are expected in the near future.

References


