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CONTRAST ECHOCARDIOGRAPHY: AN OVERVIEW OF ITS CLINICAL APPLICATIONS AND ADVANTAGES OVER THE LIMITATIONS OF NATIVE ECHOCARDIOGRAPHY AND COMPARISON OF CONTRAST ECHOCARDIOGRAPHY WITH CARDIAC MAGNETIC RESONANCE IMAGING

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Abstract:

In less than half a century echocardiography has revolutionized cardiovascular medicine. After EKG and CXR it is the most frequently performed cardiovascular exam through which information regarding cardiac morphology, function and hemodynamics can be obtained non-invasively. This technique has rapidly developed and evolved through M-mode, 2D, Doppler, stress, TE, intraoperative, contrast, digital, 3D and intra-cardiac and is being considered as a mainstay technology of clinical medicine. In 1953, Dr. Inge Elder and Dr. Helmet Hertz collaborated and began to use a commercial ultrasonoscope to examine the heart. This collaboration is accepted as the discovery of echocardiography, which was called cardiac ultrasound at that time(UCG).[1] It was in 1963,when Dr. Harvey Feigenbaum became interested in this subject and used an echoencephalography, a machine to record images of the heart rather than its original intent to record images of the brain. In 1968,Feigenbaum collaborated with Dodge at university of Alabama on the development of M-mode technology for the measurement of left ventricular diameter, and it was at this time when echocardiography was named and recognized clinically as an acceptable technique in the field of cardiology. [2] Though Transthoracic echocardiography (TEE) is the most widely and commonly performed cardiac ultrasound and has the potential to comprehensively evaluate left and right ventricular diastolic\ systolic functions, regional wall motion, valvular diseases and pericardial diseases, experts have come to realize the limitations of this technique no matter how skillful the sonographer is. Some of these limitations can be overcome using contrast agents. Contrast echocardiography is very useful when an accurate assessment of left ventricular (LV) function is required under a few circumstances like to assess LV function in patients in the intensive care, to help guide treatment decisions in heart failure patients, to keep follow up of patients with moderate valvular diseases and decision for surgical treatment, selection and monitoring of patients undergoing chemotherapy with cardio toxic drugs.

Keywords: *cardiovascular medicine, cardiac morphology, echocardiography, chemotherapy.*

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UNDERSTANDING BASIC PHYSICS LEADIND TO RAPID DEVEPOLMENTS IN CONTRAST ECHOCARDIOGRAPHY:

The reason why blood appears black on conventional 2D echocardiography is not because it produces no echo, but because the ultrasound scattered by red blood cells at conventional imaging frequency is very weak, several thousand times weaker than that of the myocardium and so here underlies the displayed dynamic range. The principle of contrast ultrasound results from the scattering of incident ultrasound at a gas/liquid interface, increasing the strength of returning signal. However, the ultrasound/bubble interaction is complex and its nature has recently been completely elucidated. The key to perform, understand and interpret a contrast echo study is to understand this interaction. When ultrasound is exposed to gas bubbles, a phenomena called insonation, the gas bubbles pulsate, with compression at the peak of the ultrasound wave and the expansion at the nadir (opposite to).Studies have shown that due to the extent of this volume pulsation the radius of gas bubbles changes by a factor of 20 or more. In an ultrasound beam with a frequency of 3 MHZ, this will result in bubble oscillation three million times per second as a result of which sound is generated and combined with that of thousands of other bubbles, results in the scattered echo from the contrast agent.[4] Distinguishing this echo, such that it can be differentiated from that of tissue, improves the sensitivity of contrast ultrasound and is the basis for new contrast specific imaging modes. With increasing power, insonation of gas bubbles can result in linear, nonlinear or bubble destruction (scintillation).This linear oscillation will augment the echo signal from the blood pool, and was the behavior originally recognized as the major source of contrast, however in reality the pressure generated by conventional ultrasound equipment greatly exceeds that required to generate linear oscillation, with nonlinear and bubble destruction as the result and this underlies the transient nature of the contrast effect with conventional and first generation contrast agents.[4,5].It was recognized that the insonated gas bubbles displayed the physical property of resonance (a frequency of oscillation at which the absorption and scattering of ultrasound is efficient).It appears to be a fortunate coincidence that gas bubbles of a size (1-5 micro m) required to cross the pulmonary vascular bed resonate at a frequency range of 1.5 – 7 MHz, precisely that used in diagnostic ultrasound. Insonation of gas bubbles at their resonant frequency results in non linear oscillation of the bubble resulting in the generation of harmonics (ultrasound produced at a frequency which is a multiple of the insonating frequency).Recognition of this property of contrast media led to the development of harmonic imaging. With the receiver tuned to receive double the transmit frequency, an image is generated predominantly from the first harmonic signal, greatly improving the signal to noise ratio. [4,5] Contrast imaging requires ultrasound machine settings to be optimized for the modality used. This requires variation in the system power output, indicated on clinical systems as the mechanical index (MI).This is an estimate of the peak negative pressure within the insonated tissue defined as the peak negative pressure divided by the square root of the ultrasound frequency.[4] To enable an estimate of the tissue effects of ultrasound exposure to be made, display of MI was made mandatory in the USA as a safety measure. As this also reflects the mechanical effect of ultrasound on a contrast bubble, this has proved useful in developing machine settings for contrast ultrasound. Though MI is not comparable from machine to machine but still it is one of the most important parameters to set correctly in a contrast echo study. Standard clinical echocardiography imaging utilizes an MI of around 1.0,but a lower setting of around 0.5 is usually optimal for left ventricular opacification. To achieve myocardial perfusion imaging the extremes of power output are utilized, high MI> 1.2 is used to achieve bubble destruction in power Doppler imaging and ultra-low MI < 0.1 is required to induce linear oscillation of microbubbles required for real time myocardial perfusion imaging.[6,4]

CONTRAST AGENTS FOR ECHOCARDIOGRAPHY:

In the beginning contrast echocardiography used free air in solution but these large, unstable air bubbles were not stable enough to cross the pulmonary vascular bed, allowing right heart contrast effects only. The first agents used for left heart contrast via intravenous route(first generation agents)were air bubbles stabilized by encapsulation(Albunex) or by adherence to micro particles (Levovist) and using fluorocarbon gas that stabilizes bubbles further due to its low solubility property (second generation bubbles e. g. Optison, SonoVue) which increases the duration of contrast further.[4,7] Third generation contrast agents though still not commercially available have known to be encapsulated by a polymer shell and contain a low solubility gas that should produce much more reproducible acoustic properties. In addtition to the strengths of the contrast agents mentioned above, they have a few more advantages like they are much safer to use than other molecular imaging modalities such as radionuclide imaging because it does not involve radiation, contrast enhanced ultrasound is cost efficient and widely available as compared to other imaging modalities like MRI,PET,SPECT which are very cosltly, moreover since micobubbles can generate such strong signals a very low intravenous dosage is required to achieve the desired effect as compared to the MRI contrast agents.

As far as the safety of these contrast agents is concerned, studies have indicated that they are among the safest contrast agents used for non-invasive immaging. It has been noticed that only one in every ten thousand patients receiving intravenous contrast agents develop serious cardiopulmonary reaction most probably due to a non-IgE mediated pseudo prophylaxis.[6] Though this scenario rarely occurs but still it is important for the laboratories to counter this issue which is appropriately done by having emergency carts with adequate equipment's and therapy, and well trained laboratory personnel. The only major contraindications to the use of contrast agents are patent foramen ovale (PFO) or previous hypersensitivity reaction to the contrast agents. Other few contraindications that vary between the contrast agents include pulmonary hypertension, pregnancy, lactation and severe liver diseases.

CLINICAL UTILITY OF CONTRAST ECHOCARDIOGRAPHY:

The foremost reason for referral to echocardiography is LV function. Assessment of LV function is extremely important and it correlates with the symptoms, prognosis, events and complications in a number of conditions. Many decisions in cardiology are based on the LV function. There are a few fundamental principles that are extremely important to understand in order to properly comprehend the LV function, which is established by estimating the ejection fraction(EF) which is a fraction\percentage of blood ejected from the ventricle during systole in relation to the total end-diastolic volume(EDV).The LV function is usually judged on the basis of how much smaller the ventricle becomes during systole. When the heart function is compromised less blood will be pumped therefore EF will fall. EF is also a function of the ventricular size like for example in athletes who have larger ventricles there EF will drop because only a small systolic reduction in ventricular size is enough to produce stroke volume (SV) to perfuse the body. On the other hand in a situation like hypervolemia the ventricle is small and the heart will compensate by increasing its contractility and therefore will have an EF higher than normal. Introduction of contrast agents in echocardiography has tremendously improved the accuracy and assessment of LV function in addition to improved delineation of the endocardial border, which will be discussed here in detail.

Quantitative assessment of LV function:

An accurate serial assessment of left ventricular ejection fraction(LVEF) and volume is critically important not only in the management but also in the prognosis of patients being reevaluated for heart failure with a change in clinical status, after myocardial infarction remodeling, after heart transplant and evaluation for the timing of surgical intervention in patients with valvular diseases, those undergoing chemotherapy or inter-cardiac device placement[8],therefore quantitative assessment of LV function must be considered in patients in whom precise information is clinically required. Although echocardiography is considered as the best suited modality for the serial assessment of cardiac function in terms of the absence of ionizing radiation, low cost, easy availability and portability, but unfortunately studies have shown that native echocardiography may have significant variability for ventricular function measurements when compared to the accepted gold standards that has limited its ability to accurately assess cardiac function.[8] Contrast enhanced echocardiography when compared with native echocardiography in several recent studies showed better agreement and a reduction in inter observer variability in measuring LV volume and ejection fraction[8,13,14],moreover the underestimation of LV volume is also nearly resolved with the application of contrast agents. All these findings support the importance of using contrast enhanced echocardiography in the serial assessment of the cardiac function.

1)Contrast enhancement in stress echocardiography and regional wall motion assessment:

A)Thorough detailed evaluation of the regional wall motion, cavity size, and LV function at rest and with stress is considered as an established and recognized tool for the diagnosis of coronary artery disease(CAD).The detection of CAD by stress echocardiography is based on the assessment of the contractile dysfunction in any of the myocardial segments at rest or with stress, therefore complete visualization of all the LV endocardial borders is necessary to exclude regional wall abnormality confidently. Interpretation of wall thickening is qualitative, is highly dependent on the skill and experience of the reviewing physician and is considerably affected by the quality of images recorded. During stress images are worse due to cardiac motion and hyperventilation, in addition to numerous other factors like obesity and lung disease.

In one study that looked at the inter-institutional observer agreement during dobutamine stress echocardiography, agreement of the presence of an abnormality on stress echocardiography was 73% of all studies but 100% when considering only images of the highest quality and only 43% for the lowest quality.[3,9] Clinical studies have shown the benefit of contrast in improving image quality, visualization of percentage of wall segments and confidence of interpretation of regional wall function both at rest and at peak stress. Therefore,it appears reasonable to use contrast routinely in stress echocardiography.

B) Contrast agents use in the intensive care unit (ICU) the coronary care unit (CCU):
It is quite reasonable to use contrast agents in such patients routinely, as they will produce the best accuracy and reproducibility in the assessment of LV function. It has been well documented that patients in the ICU and CCU often have poor acoustic windows and image quality due to several factors like hyper inflated lungs due to mechanical ventilation, lung disease, subcutaneous emphysema, surgical incision, chest tubes, bandages and poor lighting. Moreover, such patients require urgent assessment of their cardiac performance in order to make immediate management decisions. The use of contrast echocardiography overcomes several disadvantages associated with standard echocardiographic images in the ICU and CCU and can be beneficial in the assessment of LV function As the patients treated in the ICU were not included in the clinical trials for the approval of the contrast agents, therefore special warnings and absolute or relative contraindications prior to the injection of the agents in these patients have to be considered.

C) Contrast agents use for follow up of patients with moderate valvular disease and decision for surgical treatment:
Patients with moderate valvular diseases such as mitral or aortic regurgitation may prompt surgery even in the absence of symptoms therefore it is really to keep follow up of such patients for an accurate assessment of LV volume and ejection fraction. Patients with mitral regurgitation having an EF<40% and ESVD>60mm are indicative for surgery whereas patients having aortic regurgitation with an EF<55% and ESVD>55mm are candidates for surgery. As mentioned earlier, even if these patients are asymptomatic, they would require surgical intervention. Therefore, the management decisions are highly based on the findings obtained by the most accurate echocardiographic method. Thus, whenever there are any myocardial segments that cannot be delineated properly, contrast echocardiography must be considered.

D) Contrast echocardiography for the assessment of LV function to guide therapy in heart failure patients:
The accurate determination of LV ejection fraction is critically important for many patients with cardiovascular diseases and has a prognostic value for predicting outcomes in patients with congestive heart failure. For instance prophylactic implantable cardioverter-defibrillators(ICD) are approved for NYHA class 2 and 3 patients with an EF of less than 35%,the same threshold has been proposed for cardiac synchronization therapy(CRT) when there is QRS prolongation and heart failure class 3.EF can vary considerably in weekly repeated measurements and this limit can vary by about 8.5% below or above the mean calculated EF for an individual.[3,10,11,12] Although there also can be variations in the calculated EF depending on the method used. The understanding of LV volume by echocardiographic methods has been a major problem and one reason for this is the limitation due to geometric factors particularly when using one plane but even when using 3D echocardiography for calculating LV volume, the volumes obtained are significantly smaller than those obtained in MRI studies.[3,13,14] By using contrast agents the small spaces between the trabeculations are filled and consequently the contour for border tracing will include a large area than with conventional echocardiography.

E) Contrast agents use in the selection and monitoring of patients on chemotherapeutic drugs that are cardiotoxic:
Accurate assessment of EF is critically important for the selection and monitoring of patients using anti-cancer drugs. For instance, Transtuzumab which is an agent used for breast cancer treatment, according to most guidelines patients having an EF of less than 55% must not be started on Trastuzumab and those patients who are on Transtuzumab if experience a fall in EF of 10% or EF less than 50% therapy must be immediately stopped.[3] Moreover, echo labs that perform studies to monitor trastuzumab treatment have to provide yearly evidence through audits or quality control processes that the 10% EF change they identified is a true change therefore widespread use of contrast is strongly recommended.

2) Assessment of LV thrombi and masses using contrast agents:
Echocardiographic contrast agents also have been of immense value in the structural assessment of left and right ventricles and atria specially left atrial appendage, they have a key role in defining LV apical abnormalities and intracardiac masses A LV thrombus must be excluded in those patients with low EF or wall aneurysm. For the diagnosis of LV thrombus TTE is considered as the standard diagnostic procedure and has reported to have a sensitivity of 95% and a specificity of 86%.Conventional echocardiography suffers from near-field artefacts, where usually the LV thrombi are located.[3,15] Contrast echocardiography is

used as a tool to differentiate thrombi from artefacts and to improve exclusion or display of thrombi. It is also very useful in differentiating a thrombus from a tumor in which a thrombus appears as a non-calcified structure whereas tumors are seen as an opacification related to their degree of vascularization.

3)Assessment of RV dysplasia/thrombus using contrast echocardiography:
In order to assess RV volume, degree of dysplasia or the pressure of intracavitary masses it is essential to properly delineate right endocardial borders with RV trabeculations. Although no studies have shown that the findings of contrast echocardiography can match that of MRI for assessing RV function but considering results of LV function, it is likely that using contrast echo is a cheaper alternative to MRI. [3,16] Assessment of RV function using contrast agents is already the method of choice in those patients in whom MRI is contraindicated.

4) Assessment of LV non-compaction and apical hypertrophy using contrast agents:
LV non-compaction is an uncommon but increasingly recognized abnormality that can lead to heart failure and eventually death. Its pathology is related to a change in the myocardial structure with thickened and hypokinetic segments that consists of two layers, a non-compacted, trabeculated, subendocardial myocardium and a thin compacted sub epicardium myocardium. It is easy to misdiagnose this disease as the compacted layer often resembles a thickened myocardium, especially in patients with sub-optimal images.[3] Using contrast the two myocardial layers can be clearly visible and a ratio of 2:1(measuring the thickness of the non-compacted to the compacted) has been proposed. Therefore, for these reasons it appears sensible to use contrast agent's despite of the image quality.

LV apical hypertrophy is associated with hypertrophic cardiomyopathy and is quite often missed on routine echocardiography because of incomplete visualization of the apex. When apical hypertrophy is suspected but not clearly excluded or documented, contrast study must be performed. Characteristic findings of apical hypertrophy on contrast echocardiography is a spade-like appearance of LV cavity with marked apical myocardial wall thickening.[8]

COMPARISON OF CONTRAST ECHOCARDIOGRAPHY AND CARDIAC MAGNETIC RESONANCE IMAGING:

A number of studies have been performed in the past comparing echocardiography and cardiac magnetic resonance (CMR) for the definite measurements of LV volume and EF, majority of which have used 2D echocardiography for the analysis of LV volume and EF. Most of these studies have been performed in the single-center settings with single readers. [13,14,18,19] A meta-analysis performed recently showed that 3D echocardiography resulted in slightly larger LV volumes than 2D echocardiography whereas EF was found to be similar. Administration of contrast showed improved accuracy and reliability of LV volume and functional measurements that were demonstrated in single-centre as well as multi-centee 2D echocardiographic based studies. These studies showed that the EF assessment by echocardiography was similar compared with CMR for contrast enhanced as well as unenhanced imaging, but LV volumes were found to be too low when compared with CMR even with contrast.[13,20] Geometric assumptions and foreshortening of the left ventricle have been considered to be the reason for such an underestimation by 2D echo, though 3D echo has been reported to improve accuracy in the assessment of LV volume.

Another multi-centre study conducted recently demonstrated that LV volumes on 3D echo were not greater when compared with those by 2D, which was in contrast to most single-centre studies. Administration of contrast with 3D echo in the same multi-center study showed larger LV volume compared with unenhanced echo and less underestimation compared with CMR.[13] This finding was in agreement with a single-centre study of 20 patients that demonstrated improved accuracy on volume measurements compared with CMR with contrast echocardiography.[13,21] Therefore, to minimize the difference in volume measurements compared with CMR, contrast administration should be considered when 3D echo is used.

The assessment of EF in the same multi-center study showed only moderate agreement with CMR when compared to unenhanced echocardiography, whereas contrast administration increased the correlation and reduced the limits of agreement with CMR. Though 2D and 3D echocardiography did not change the average assessment of EF, contrast administration with 2D as well as 3D echo resulted in a reduced bias of EDV and ESV and improved correlation when compared with CMR.[13]

Supplementary data:
Can be found online, http://en.wikipedia.org/contrast-enhanced_ultrasound
https://123sonography.com/node/855

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