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RESEARCH ARTICLE

CONTRAST ECHOCARDIOGRAPHY: CURRENT APPLICATIONS AND INNOVATIONS

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Abstract

The ability to opacify the left ventricle and delineate the endocardium after intravenous injection of microbubble ultrasound enhancing agents (UEAs) is of established value to quantify volumes and function in suboptimal unenhanced images, particularly in stress echocardiograms. However, applications other than quantitation of left ventricle structure and function are being used in myriads of other disease states for contrast enhanced left ventricular opacification. Contrast agents enable recording of Doppler velocity signals in patients with poor ultrasound transmission, providing estimates of aortic stenosis gradient and pulmonary artery pressures. Contrast echo is of value in detecting apical hypertrophic cardiomyopathy and accompanying apical aneurysms. Most importantly, ultrasound enhancing agents can identify apical and left atrial masses when they cannot be visualized in unenhanced images, and can distinguish thrombi from tumors by visualizing the vascularity inherent in tumors. Contrast agents distinguish trabecular from compacted myocardium in noncompaction syndrome, and hypertrabeculation with other abnormal conditions. A major potential application of UEAs is myocardial opacification, which can assist in identifying nonviable myocardium. Also, the delayed reappearance of myocardial perfusion after microbubble destruction identifies impaired contrary flow and can diagnose coronary stenosis. Innovative applications of ultrasound contrast agents currently under investigation, include visualizing the vaso vasorum to identify plaques and assess their vulnerability, and theranostic agents to deliver drugs and biologists and to assist in sonothrombolysis. It is anticipated that the role of ultrasound contrast agents will continue to increase in the future.

Introduction:-

Drs. Gramiak and Shah (1969)were the first to track the cloud of echo signals produced by the left atrial injection of indocyanine green opacifying the left atrium and subsequently the aorta by m-mode echocardiography [1]. Subsequently, contrast echocardiography consisted of the injecting microbubbles produced by agitating saline which opacified the right ventricle. The development of microbubbles using heavier molecular weight and less diffusible gases surrounded by a shell comprised largely of albumen lipoproteins efficiently persisted in circulation to cross the lungs and opacify the left sided cardiac chambers. They effectively and accurately delineate the endocardial border,

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an ability of paramount importance in patients with technically suboptimal images. There are currently a number of UEAs approved for this application (Table 1) and the safety of the procedure has been well established. Left ventricular opacification with UEAs has achieved an established role in clinical echocardiography and is currently applied routinely on a daily basis to define the endocardial border and assess left ventricular dimensions and contraction.

Table 1:- Ultrasound Enhancing Agents.

Agent	Mean size (u)	Gas	Shell
Levovist	2-3	Air	(Galactose)
Optison	4.7	Perflouropropane	Albumin
Definity	1.5	Perflouropropane	Phospholipid
Imagent	5.0	Perflourohexane-N	Surfactant
Lumason (Sonovue)	2.5	Sulfur hexaflouride	Phospholipid
Cardiosphere	4.0	Nitrogen	Polymer
Acusphere	2.0	Perflourocarbon	Polymer

A number of studies have demonstrated the ability of contrast enhanced echocardiograms to yield measures of left ventricular volume and ejection fraction that correlate well with other techniques such as magnetic resonance imaging in patients in whom the unenhanced echocardiogram is technically inadequate [2, 3]. Thus, administration of contrast agents can successfully identify the endocardial border in patients in whom endocardial targets cannot be imaged with unenhanced images. Of perhaps greatest importance, left ventricular opacification with ultrasound enhancing agents has been documented to be capable of impacting the management of patients with known or suspected cardiovascular disease [4].

UEAs may also be of value in defining endocardial landmarks on three-dimensional echocardiography which is less sensitive in imaging low intensity targets than conventional two-dimensional imaging.

Despite documentation that ventricular opacification by contrast echo could accurately identify left ventricle volumes and ejection fraction and thereby influence patient management, implementation of these recordings in echo laboratories has been slow and variable. Evidence exists to indicate that, although 15% -30% of echocardiographic studies are marginal or inadequate, especially stress echo and those performed in the intensive care unit, only approximately 5% of echo studies employ ultrasound enhancing agents [5]. A number of factors appear to contribute to this underutilization, such as the need to do an intravenous injection and the legacy mindset of interpreting echocardiograms for years without the benefit of contrast visualization. This has led to an attempt to define those patients in whom UEAs should be applied in their echocardiogram Obvious candidates include patients with obesity, chronic obstructive pulmonary disease, chest deformities, and any patient in whom acoustic windows are limited to yield adequate images. An important application of left ventricular opacification has been to increase the reproducibility of echo quantification of left ventricular size and contraction. It has been demonstrated that the use of UEAs and markedly reduced variability in echo quantification and yield measurements of echocardiographic size and function to reproducibility is comparable to that of other techniques such as magnetic resonance imaging [6, 7]. Based upon these data, the guidelines for contrast utilization of the American Society of Echocardiography recommend the use of UEAs in all patients undergoing rest echocardiograms for the indication of evaluation of left ventricular systolic function, not just those in whom images are technically inadequate [2]. The criteria for determining that studies are technically inadequate include the inability to visualize the endocardial border in two or more contiguous segments of the left ventricle in unenhanced images. Obviously, since abnormal contraction of even one left ventricular segment on a stress echocardiogram establishes an abnormal study, the indication for contrast enhancement in this setting is considerable.

Over the last two decades, regardless of advances in cardiac imaging technologies, echocardiography has sustained its leading role as a diagnostic tool in cardiovascular medicine. The foremost reason is because of its unique advantages comprising versatility, portability, rapid availability even at the bed side, excellent temporal resolution, elucidation of images in real time, comparatively low cost and above all no risk of exposure to radiation. In multiple clinical situations 2Dimensional echocardiography (2DE) is operated for imaging in OPD clinics, indoor wards, intensive care units, operation theatres and faraway locations.

Notably, in the current era there has been an exponential increment in the applications of contrast echocardiography with the emergence of newest second generation UEAs [8]. It is noteworthy that because of relentless investigations and research in the area of contrast echo, several innovative and state-of-the-art techniques are evolving for the wider implementation of this outstanding invention. A comprehensive recommendations has been proposed by the American Society of Echocardiography [8] regarding the usage of this highly skillful technique.

While the ability to enhance endocardial border definition by contrast echo is well established and integrated into practice, a number of other applications other than border definitions are often encountered.

Application of ultrasound enhancing agents

Contemporary clinical applications of left ventricular (LV) and vascular opacification for augmentation of contrast images in myriads of cardiovascular diseases are enumerated below:

1. Endocardial border definition of LV (Figure 1A)
2. Estimation of LV ejection fraction (LVEF), dimensions and volumes (Figure 1B).
3. Enhancement of doppler recordings (Figure 1C).
4. Amplification of regional wall motion abnormalities at rest (Figure 1D).
5. Amplification of regional wall motion abnormalities during stress (Figure 1E).
6. Delineation of Apical hypertrophic cardiomyopathy (Figure 1F), Non compaction cardiomyopathy (Figure 1G), LV thrombus (Figure 1H), Eosinophilic cardiomyopathy (Figure 1I) and LV pseudoaneurysm (Figure 1J).
7. Discernment and characterisation of non-thrombotic masses (Figure 1K).
8. Unmasking of aortic dissection (Figure 1L).
9. Myocardial contrast echocardiography (Figure 1M).
10. Myocardial perfusion imaging (Figure 1N).

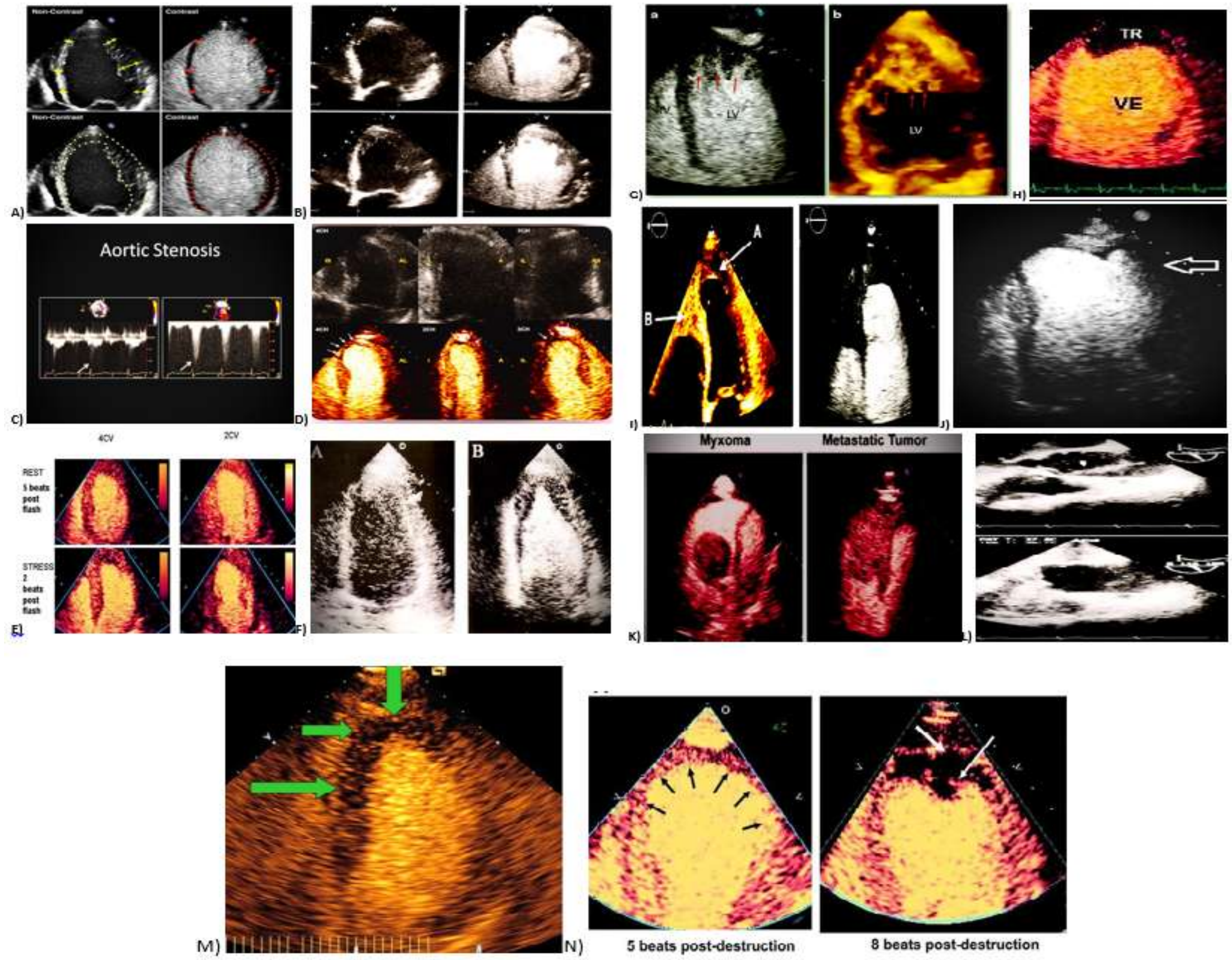

Figure 1:- A) LV border border definition, Left panel shows the unenhanced 4CH view in a patient of dilated cardiomyopathy before contrast enhancement while the right panels after administration of contrast agents exhibit the apparent endocardial border of entire LV. B), Evaluation of LV volumes and ejection fraction by contrast echocardiography; Estimation of end-diastolic (top) and end-systolic (Bottom) images of the 4 CH view from a patient before (left) and after (right) intravenous contrast. C), Continuous wave spectral Doppler of a patient with severe aortic stenosis. (Left), unenhanced image with weak tracing unable to confirm maximal gradient > 30 mmhg (arrow). (Right), contrast enhanced image of the same patient confirms a maximal gradient > 70 mmhg. D) Identification of segmental wall motion abnormalities at rest. TTE of a patient comparing standard views (above panels) with myocardial contrast echocardiogram images (lower panels). Myocardial contrast echocardiogram wall motion and myocardial perfusion abnormalities in mid-to-distal septum, the apical and apico-lateral wall (see arrows). E) Identification of LV segmental wall motion abnormalities after stress stress. On the 4CH view, an apical and basal inferno-septal defect are evident 2 beats post stress. On the 2 CH view there is hypoperfusion of inferior wall and an apical defect on the post stress images. This is consistent with multi- vessel coronary artery disease. F) Detection of apical hypertrophic cardiomyopathy. On the left panel is the image of non- diagnostic TTE in 4CH view and on the right panel, after Intravenous contrast injection a distinctive image of apical hypertrophic cardiomyopathy is revealed. G) Detection of Noncompaction cardiomyopathy by contrast echocardiography. On the left panel in 4CH view deep recesses in the noncompacted LV apex (red arrows) are discerned. On the right panel a 3D reconstruction of the same image illustrates the extent of the noncompacted area .The red arrows point to the entrance points of the sinusoidal recesses in the noncompacted apical myocardium. H), delineation of LV apical thrombus in 4CH view. TR- thrombus, VE- left ventricle. I), Eosinophilic Cardiomyopathy detection by contrast

echocardiography. On the left panel there is presence of marked endocardial thickening of LV (arrow A) as well as obliteration of right ventricular (RV) apex (arrow B). Similar findings are obtained in black and white image. J), Detection of LV pseudoaneurysm by contrast echocardiography. In the 4CH view an arrow is seen pointing towards the whole outer margin of LV pseudoaneurysm. K), Detection of LV non thrombotic masses by contrast echocardiography. In the modified 4CH view. In the left panel is the presence of myxoma and the right panel portrays metastatic tumor. L), Detection of Aortic dissection by contrast echocardiography. There is presence of ascending aortic dissection flap and the contrast agent delineated the true and false lumen adequately. M), In the 4CH view myocardial contrast Echocardiography demonstrates the delayed contrast enhancent in the distal septum and apex of LV (green arrows) compared to the proximal septum and lateral wall. N), Myocardial Contrat Perfusion Echocardiography. On the left panel a normal perfusion is seen in a patient of apical ballooning(black arrows) and on the right panel a dense apical defect is visualised in a patient of anterior myocardial infarction(white arrows).

Keeping pace with the advancement of technology and artificial intelligence (AI) newer, innovative and ultra-sophisticated applications of UEAs are underway both for diagnosis and therapy of cardiovascular pathologies [9, 10]. Several ingenious, futuristic and pioneering endeavours which are on the horizon are mentioned:

1. **Molecular Imaging -**Non-invasive molecular imaging (MI) can yield extremely precise diagnosis. MI employing contrast enhanced ultrasound (CEU) is a scientific maneuver that relies on ultrasound (US) identification of microbubble contrast agents to target the molecular or cellular phenomenon that originate at the interface of blood pool and endothelium. A distinctive knowledge is accomplished on ischemia (Figure 2A), atherosclerosis, angiogenesis, reperfusion injury, thrombus formation, vascular injury and swelling. Correspondingly, MI guides the appropriate therapy based on vascular phenotype.
2. **Contrast-enhanced ultrasound imaging of intraplaque neovascularisation** -Neovascularisation assessed by CEU imaging is associated with plaque echolucency, a well accepted marker of high risk lesions, and does not depend on the degree of stenosis. CEU imaging may identify highly vascularised potentially vulnerable plaques, and furthermore, may therefore be a new tool for plaque risk stratification, beyond the simple evaluation of stenosis and echogenicity, and for the assessment of progression and regression of atherosclerosis. Till date the research has been directed towards the carotid artery plaques (Figure 2B), nonetheless, in future, CEU imaging may be a novel technique for detection of vulnerable plaques in the coronary arteries causing acute coronary syndrome.
3. **Therapeutic contrast echocardiography-** It has been recently reported that transthoracic high mechanical index (MI) impulses from a diagnostic ultrasound transducer (DUS), during an intravenous microbubble infusion (sonothrombolysis) can restore epicardial and microvascular flow in acute ST-segment elevation myocardial infarction (STEMI) (Figure 2C, 2D), The effect of sonothrombolysis were recognised early in the treatment period before emergent PCI, but resulted in sustained improvements in systolic function and reduced the need for defibrillators at 6-month follow up.
4. **Intracavitary blood flow patterns -**
   - vortex formation (Figure 2E)
   - energy dissipation
   - resonance time to LV diastolic filling are being investigated in normal and pathological states.
5. **Bioeffects of ultrasound -**Presently microbubble cavitation, convective motion and microstreaming have been employed to evoke increased permeability of vessels for extravascular expatriation of medications and genes (Figure 2F). This will result in simultaneous concentration of shear related bioeffects through UEAs. Correspondingly, it would augment tissue perfusion in coronary artery disease and ultimately reduce the infarct size, in patients of STEMI undergoing primary PCI.

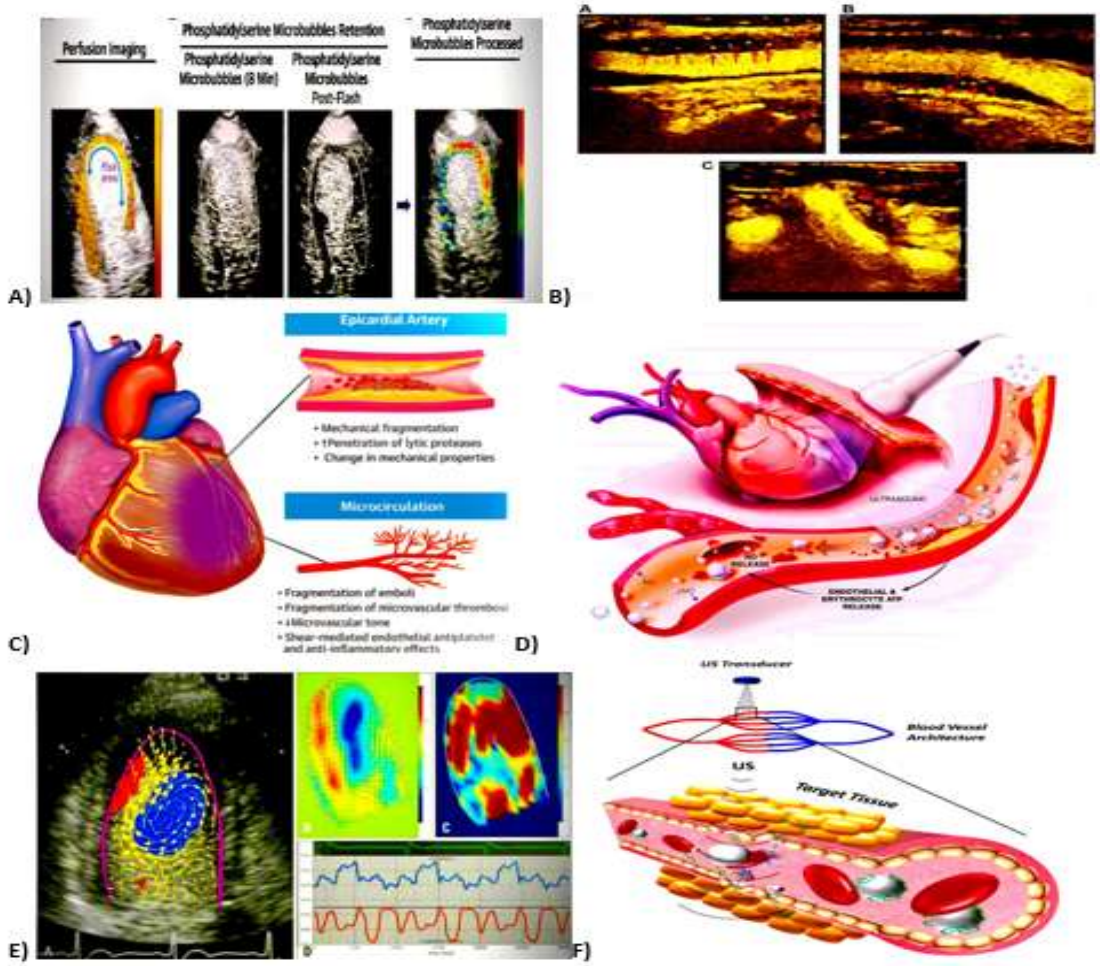

Figure 2:- A), Molecular Imaging by myocardial contrast echocardiography in subjects with Acute Coronary Syndrome. B), Carotid intraplaque neovascularisation detected by contrast enhanced ultrasound was localized to plaque shoulder and was an independent predictor of cardiovascular events in patients undergoing stress echocardiography. C), Putative Biological Mechanism for myocardial size reduction by contrast ultrasound cavitation. The image is a schematic illustration of the broad effects that microbubble cavitation could potentially exert at the level of epicardial arteries and microcirculation. D, Sonothrombolysis for STEMI, restoration of epicardial and microvascular blood flow in STEMI using sonothrombolysis. E), LV vortex flow (a), analysed by contrast echocardiography using particle image velocimetry method, (b), Parametric representations of steady streaming field, c), pulsatile strength field,(d), and vortex size change throughout the cardiac cycle. F), Schematic representation of how microbubble cavitation facilitates DNA (green) extravasation into tissue.

Conclusion:-

Standard 2Dimensional echocardiography maybe often suboptimal falsely negative or inconclusive, even though it is currently considered an indispensable tool for a contemporary non-invasive cardiovascular facility. It is specifically meant to generate exceptional information which increases the diagnostic presentation and moreover provides credence to the reader, in particular. Contrast echocardiography necessitates knowledge of the recent protocols and the robust echocardiography workroom policies that determine the quality, efficiency and safely of the procedure.

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