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The use of transpulmonary contrast echocardiography – a first experience in Serbia

Upotreba transpulmonalnog ehokardiografskog kontrasta – prvo iskustvo u Srbiji

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Abstract

Background/Aim. Contrast echocardiography (CE) is an echocardiographic modality where ultrasound contrast echocardiographic agent (CEA) is introduced peripherally for the image enhancement. The aim of this study was to present the initial clinical experience of the use of CEA Optison™ (GE Healthcare, Princeton, NJ) at the Institute for Cardiovascular Diseases of Vojvodina, Serbia and prospectively monitor the occurrence of possible side effects. **Methods.** A total of 357 patients were referred for resting or stress echocardiographic examinations, with an approved indication for CEA administration. The average age of patients was 63.3 years (range, 21–92 years), 62% of them were men. Most of the patients (77.31%) had some form of ischemic heart diseases. Hypertension was the most frequent risk factor (77.03%), but 57 patients had diabetes mellitus and 33 patients had chronic kidney disease as comorbidity. Most (90.5%) of the patients were on beta blocker therapy, 83.5% of them on angiotensin converting enzyme/angiotensin receptor blockers. Majority (80.3%) of the patients received single or dual (49.5%) antiagregation therapy, 74 (26.3%), of them were on anticoagulation therapy, 55.1% of the patients were taking diuretics. The global ejection fraction (EF) was preserved in 39.85% of them, the majority (136 of them), had left ventricle (LV) impairment, with an EF less than 50%. Patients were followed up for 30 minutes after CEA administration for potential side effects. In 118 patients, vital signs (heart rate, oxygen saturation, body temperature, systolic and diastolic blood pressure) were measured before and 30 minutes after CEA administration. **Results.** The administration of CEA was not associated with side effects. Diastolic blood pressure drop and heart rate increase were statistically, but not clinically significant (p = 0.027 and p = 0.028, respectively). **Conclusion**. Changes in analyzed vital signs were clinically non relevant. CE is a safe noninvasive diagnostic modality for patients undergoing rest and stress echocardiography.

Key words:
adverse drug reaction reporting systems; cardiovascular diseases; comorbidity; contrast media; echocardiography.

Apstrakt

Uvod/Cilj. Kontrastna ehokardiografija (CE) je dijagnostička metoda koja podrazumeva aplikaciju kontrastnog agensa (CEA) u perifernu venu u cilju poboljšanja ehokardiografske slike. Cilj rada bio je, da se prikaže inicijalno iskustvo upotrebe Optisona™ (GE Healthcare, Princeton, NJ) kao CEA u Institutu za kardiovaskularne bolesti Vojvodine, Sremska Kamenica, Srbija, kao i prospektivno praćenje pojave eventualnih neželjenih efekata. **Metode.** Procedura CE je urađena kod 357 bolesnika kod kojih je postavljena indikacija za primenu CEA u miru i/ili testu stres ehokardiografije. Prosečna starost ispitanika je bila 63,3 godine (u opsegu 21–92 godine), među kojima je bilo 62% ispitanika muškog pola. Ispitanici su imali različite kliničke dijagnoze, ali najveći broj bolesnika (77,31%) imao je neku formu ishemijske bolesti srca. Hipertenzija je bila najčešći faktor rizika kod ispitanika (77,03%), a od komorbiditeta, šećerna bolest je bila prisutna kod 57 bolesnika, a 33 bolesnika je imalo hroničnu bubrežnu insuficijenciju. Većina bolesnika

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(90,5%) je uzimala beta blokatore, a 83,5% je koristilo inhibitore angiotenzin konvertujućeg enzima (ACE) ili blokatore angiotenzinskih receptora. Monoterapiju je dobijalo 80,3%, a dvojnu antiagregacionu terapiju 49,5% bolesnika, dok je 74 (26,3%) bolesnika dobijalo antikoagulantnu terapiju. Diuretike je koristilo 55,1% bolesnika. Sa očuvanom globalnom ejekcionim frakcijom (EF) leve komore (LK) bilo je 39,85% bolesnika, a većina (njih 136) je imala smanjenu EF LK (manju od 50%). Nakon primene CEA, bolesnici su praćeni još 30 minuta zbog moguće pojave neželjenih efekata. Kod 118 bolesnika su pre i 30 minuta nakon davanja CEA praćeni vitalni parametri (frekvencija srca, saturacija krvi kiseonikom, temperatura tela, sistolni i dijastolni krvni pritisak). **Rezultati.** Nakon primene CEA nisu zabeležene nuspojave. Zabeleženi su statistički značajno, ali ne i klinički značajno, smanjenje dijastolnog krvnog pritiska (p = 0,027), kao i povećanje frekvencije otkucaja srca (p = 0,028). **Zaključak.** Promene praćenih vitalnih parametara nemaju klinički značaj. CE je sigurna neinvazivna ehokardiografska metoda za pacijente podvrgnute CE u miru i testu stres ehokardiografije.

Ključne reči:
lekovi, neželjeno dejstvo, sistemi za izveštavanje; kardiovaskularne bolesti; komorbiditet; kontrastna sredstva; ehokardiografija.

Introduction

Today, echocardiography is growing side by side with modern technology and achievements in the field of other noninvasive modalities. Contrast echocardiography (CE) is a simple method where transpulmonary contrast echocardiographic agent (CEA) is introduced peripherally for the image enhancement. The clinical use of CE is defined both by the European Association of Echocardiography and by the American Society of Echocardiography (ASE) [1, 2].

The initial use of the CE were in technically difficult or uninterpretable echo images [3]. The first indication for the use of CE was to enable the visualisation of the endocardial border of the left ventricle (LV) when two or more contiguous segments were not seen well with native-noncontrast echocardiography [4].

Studies demonstrated the efficiency and safety of CEA improving the diagnostic utility of both rest and stress echocardiography (SE) [5–8].

For transpulmonary CEA, the indication in clinical cardiology is the enhancement of the left ventricule (LV) endocardial border, accurate and repeatable measurements of volumes, global and regional LV function, especially in patients who are candidates for chemotherapy, to establish the diagnosis of apical hypertrophy, LV thrombus or other intracardiac mass evaluation, noncompaction cardiomyopathy (CMP), to assess myocardial perfusion (MP) in rest and in multiparametric SE studies to assess coronary flow reserve (CFR) and/or viability, too [1, 2, 9].

The contraindications in nonpregnant adults are allergic reactions to the components of the CEA, precaution is recommended for patients with pulmonary hypertension (PH) and right to left (R-L) shunts. Side effects are rare and usually not serious [1, 2].

CE reduced intra- and interobserver variability in echocardiography interpretation, medical costs, mortality, and exposure to the ionizing radiation that is associated with other imaging modalities. The applications in research and off-label indications are also growing [1, 2].

The aim of this study was to present the initial experience after application of Optison™ (GE Healthcare, Princeton, NJ) as a CEA in routine medical practice at the Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia.

Methods

This observational prospective study was conducted from March 2017 to November 2019 at the Institute of Cardiovascular Diseases of Vojvodina in Sremska Kamenica, Serbia. During this period, a total of 357 patients with technically difficult echocardiographic examinations underwent CE. Informed consent was obtained from all patients. Data collected from each subject included demographic characteristics, history of illness, and information on allergies.

Patients with known hypersensitivity to perflutren, blood products, or albumin as well as individuals with previous history of food allergies were not included in the study. The presence of any infection or fever was also excluding criteria. Clinical diagnoses, risk factors and comorbidities, medications of the patients, LV ejection fraction (EF) and indications for CE are shown in Table 1.

CE was performed using ultrasound machines (GE Vivid 9 and VividXPRo) equipped with broadband transducers and low-mechanical index (MI) contrast-specific presets. The recommended MI in this diagnostic procedure is 0.2 or lower, which was used in this study.

In this study, CEA (Optison™), as an injectable sterile suspension, was used which consisted of microspheres filled with perflutren gas with a shell of human serum albumin.

Baseline native echocardiography was always performed before CE.

Preparation and administration of CEA required attention to the storage, preparation and application. The glass vials of the CEA were stored in a refrigerator with temperature between 2–8 °C. The preparation protocol and the administration method followed the instruction given by the manufacturer [3]. Adherence to the prescribed preparation protocol is crucial for good image quality. Optison™ was always applied as a bolus injection in this study, the amount of the CEA in the syringe was gently agitated immediately before the application after it exceeded a room temperature.

Patients were prepared and inserted with i.v. canulla with at least 20 gauge with the 3-way stopcock into the peripheral vein, usually into the right arm. The rate of the iv. bolus did not exceed 1 mL per second, flushed with 10 mL saline.

Table 1

Clinical characteristics of patients underwent contrast echocardiography (CE)

Characteristics	Values
Total number (%)	357 (100)
Gender, n (%)	357 (100)
male	244 (68.3)
female	113 (31.7)
Age (year), mean ± SD	63.28 ± 11.40
BSA (m^2), mean ± SD	1.99 ± 0.22
Clinical diagnoses, n (%)	357 (100)
ischemic heart diseases	276 (77.31)
rhythm disturbances	101 (28.29)
patients with pacemakers, ICD or CRT	21 (5.88)
cardiomyopathies	85 (23.81)
congenital and valvular heart diseases	96 (26.89)
Risk factors and comorbidities, n (%)	357 (100)
hypertension	275 (77.03)
diabetes mellitus	59 (16.53)
chronic kidney disease	33 (9.24)
obstructive lung diseases	17 (4.76)
Medications of the patients receiving CE, n (%)	285 (100)
ACE inhibitors/AT blockers	238 (83.5)
beta blockers	258 (90.5)
statins	210 (73.7)
dual antiagregation therapy	141 (49.5)
aspirin	229 (80.3)
anticoagulant therapy	74 (26.3)
diuretics	157 (55.1)
Ca antagonists	41 (14.4)
EF LV (%), n (%)	332 (100)
< 40	96 (28.9)
40–50	104 (31.3)
> 50	132 (39.8)
Indications for transpulmonary CE, n (%)	357 (100)
better endocardium delineation	82 (22.97)
LV EF estimation	31 (8.68)
apex of the LV (parietal thrombus)	59 (16.53)
hypertrophy of the LV	10 (2.80)
congenital heart diseases with or without bubble test	10 (2.80)
intracavitary mass/other then LV apex	6 (1.68)
suspected aortic dissection	3 (0.84)
transoesophageal echocardiography	4 (1.12)
SE (dobutamine, adenosine and dobutamine, pace maker, exercise)	152 (42.58)

SD – standard deviation; ACE – angiotensin converting enzyme; BSA – body surface area; ICD – implantable cardioverter defibrillator; CRT – cardiac resynchronization therapy; AT – angiotensin receptor; EF – ejection fraction; LV – left ventricle; SE – stress echocardiography .

The administered doses of CEA in our study were not specified in most of the patients, the bolus injection of the CEA was 0.3 or 0.4 mL iv. followed by a 10 mL slow saline flush. The maximum total dose did not exceed 1.5 mL, whenever the image was acceptable; the dose of the Optison™ was repeated, except in SE studies where usually at least two bolus doses were given, during the resting phase and in the peak phase. The administered doses of Optison™ were effective, sufficient to opacify the LV cavity and endocardial border in all cases of resting and SE.

Statistical analysis

Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as frequencies in percentages. Statistical significance was calcu-

lated by the Student's *t*-test and $p < 0.05$ and was considered statistically significant.

Results

The average age of patients was 63.28 ± 11.40 years, the youngest patient was 21 and the oldest one 92 years old. More than two thirds of patients were men (68.3%).

The patients who were referred for routine resting or SE examinations with an approved indication for CEA administration, fulfilled at least one of the indications listed in Table 1.

Most of the patients (77.31%) had some form of ischemic heart diseases (IHD). Rhythm disturbances, CMPs, congenital and valvular heart diseases were also present among the tested patients. Since CE was introduced, apical hypertrophic CMP was newly diagnosed in 3 of them.

Patients were with a large number of comorbidities (Table 1).

The first line indications were: better delineation of the LV endocardium, estimation of the LVEF and better evaluation of the apex of the LV.

In 3 of the patients, when CE was introduced, apical hypertrophic CMP was newly diagnosed. One patient was diagnosed with CE successfully with LV diverticulum.

Most of SE studies were indicated for patients with previous history of IHD and chest pain. Exercise, pace maker (PM), dobutamin and adenosine SE were performed with Optison™. There were 2 CE exercise SE for valve diseases-mild aortic stenosis, and for congenital heart diseases, by which two patients had corrected transposition of the great arteries. In 4 patients the indication for Optison™ administration was the left auricle exploration before electroconversion. In patients with suspected aortic dissection, the diagnoses were excluded 3 times with CE, and in one patient the dissection was confirmed with CE.

Patients were followed up for 30 minutes for any side effects and symptoms as flushing, headache, chest pain, back pain, skin rash, palpitations, dyspnea, nausea, vomiting, dizziness or vertigo. None of these or other adverse effects (AE) or side effects were present in our group. No allergic or anaphylactoid reactions occurred.

In 118 patients, vital signs (heart rate, oxygen saturation, body temperature, systolic and diastolic blood pressure) were measured before and 30 minutes after the CEA administration (Table 2).

The average systolic and diastolic blood pressure was lower after the administration of Optison™. The diastolic blood pressure drop and the heart rate increase for 4.7 beat/min (on average) were statistically significant ($p = 0.027$ and $p = 0.028$, respectively) but clinically irrelevant.

The other followed up parameters were not significantly different after the 30 minutes monitoring time in this patients subgroup.

Figure 1 shows CE in a patient with large parietal thrombus which is presented as avascular, black formation at the LV apex, on transthoracic four chamber view.

Table 2

Vital parameters before and after the administration of contrast echocardiographic agents in 118 patients

Parameters	Before (mean ± SD)	After (mean ± SD)	*p*
Systolic BP (mmHg)	125.8 ± 14.93	123.5 ± 15.41	0.208
Diastolic BP (mmHg)	72.5 ± 10.05	69.9 ± 8.88	0.027
Heart rate (beat/min)	74.9 ± 12.27	78.6 ± 16.76	0.028
Oxygen saturation (%)	96.8 ± 1.95	96.7 ± 3.10	0.373
Body temperature (°C)	35.8 ± 0.55	36.3 ± 0.47	0.434

SD – standard deviation; BP – blood pressure.

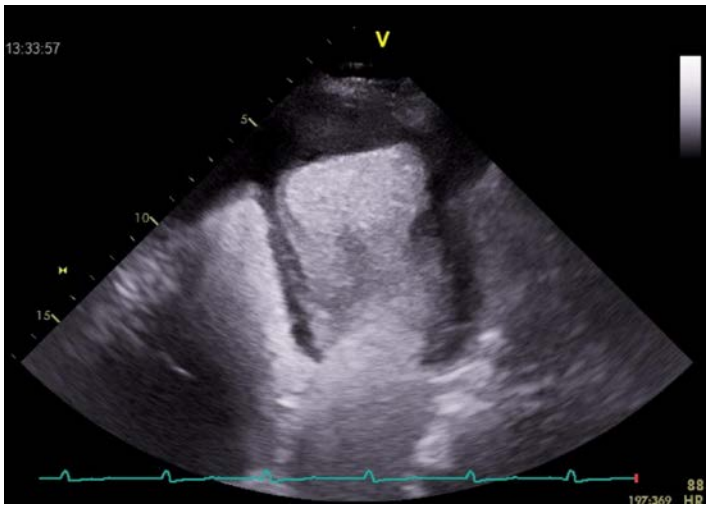

Fig. 1 – Contrast echocardiography shows large parietal thrombosis which is shown as avascular (block) formation at the left ventricle apex on transthoracic four chamber view.

In our investigated cohort, in 3 of patients, apical hypertrophic CMP was newly diagnosed by using CE (Figure 2). Two of them were more than once underwent coronary angiography for the previous IHD suspicion.

With the use of CE, the LV diverticulum was successfully diagnosed in one patient (Figure 3). It was done in dextrocardiac patients and with corrected transposion of the great arteries but none of them had a R-L shunt.

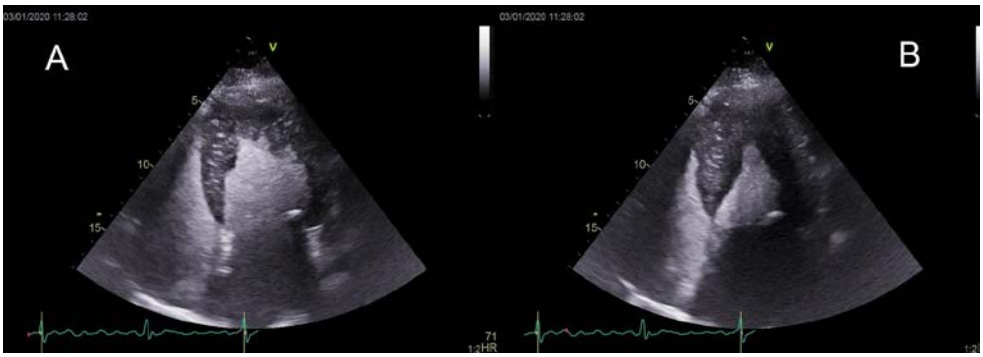

Fig. 2 – Contrast echocardiographic finding of newly diagnosed apical hypertrophic cardiomyopathy.

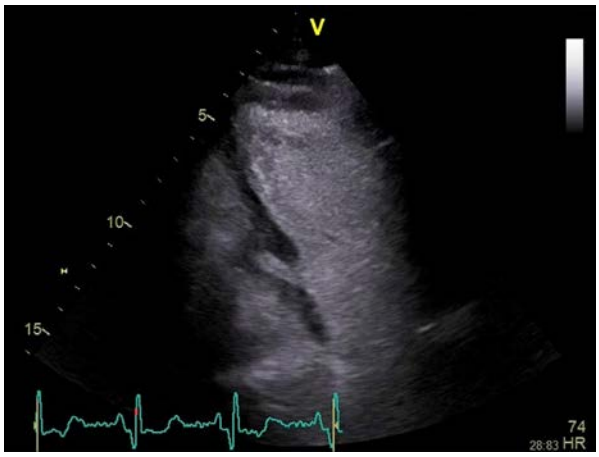

Fig. 3 – Left ventricle diverticulum in dextrocardiac patient diagnosed using contrast echocardiography.

Discussion

Today, there are three new, commercially available echocardiographic contrast agents (ECA): Optison™ (GE Healthcare Princeton, NJ), Lumason™ (Bracco) and Definity™ (Lantheus) in Europe and North America, and all of them are approved for use by the Food and Drug Administration (FDA) for the indication of LV opacification (LVO) in adults [1, 2].

The Levovist™ (Schering AG, Berlin, Germany) was the first commercially available ECA [10]. Initially, the idea was to use it in the patients with poor acoustic window or uninterpretable images [4, 5].

Currently, Optison™ is the only available CEA in Serbia. Its routine administration started at the Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica in 2017, after the project was accepted and approved by the Local Government [12]. The regulatory documents and the permission for this method were obtained from the Republic Ministry of Health.

Optison™ is a sterile, nonpyrogenic suspension of microspheres or microbubles-filled with perflutren gas in albumin shell, that are small and stable enough to pass the pulmonary circulation during the ultrasound imaging procedures. The microbubles create an echogenic contrast effect in the blood, so this imaging modality is called transpulmonary CE [3].

It is used mostly for the LVO, for segmental or global LV wall motion analysis and for identification of cardiac masses. The indications of CE are defined by the European Society of Echocardiography and ASE [1, 2, 9, 11].

A review on the safety of CEA compared to the other commonly used radiology contrast agents pronounced them safe, reliable and radiation-free diagnostic modality [7, 8].

To perform CE, in addition to CEA it is necessary to possess an ultrasound machine equipped with adequate, low MI contrast software. The MI stands for the measure of the power generated by the transducer during the echocardiographic examination.

Side effects of CEAs are rare and usually not serious, but the administration can be associated with flushing, headache, nausea, vomiting, dyspnea, chest or back pain. The albumin component of the Optison™ is a derivative of human blood, so allergic or anaphylactoid reactions can be expected although very rarely [3].

The incidence of an anaphylactoid reaction from CEA exposure was estimated at about one in 15,000 [13], so our sample size could not be able to detect such rare events.

According to the recommendations, both "physicians and sonographers who wish to perform CE, should receive training in interpretation and operational details". The antiallergic drugs and the resuscitation equipment have to be available in case of emergency [1, 2].

In our patients, systematic preprocedural detailed history was taken with special care to those allergic to proteins (blood products, food or some medications). With positive history data or even in case of a suspected allergy or elevated temperature, the patients were not given CEA, what probably increased safety.

We were eager to experience the advantage of CE in the real clinical work, but safety was our great concern in various clinical settings, having in mind that Optison™ has been available since 2017, but it is still not registered in Serbia. For this reason safety was, if not more important, but as important as the diagnostic efficacy of the CEA.

The investigated patients were indicated in accordance with the latest recommendations [1, 2]. More than two thirds of them had low EF LV, some of them had acute IHD and congestive heart failure, but all of them tolerated Optison™ well. In other reports [14, 15], a low serious side effects rate of 0.01% was noted in those patients that received CEAs.

Patients included in our study represent those who are seen daily in echocardiographic laboratories, with a high frequency of cardiac risk factors and comorbidities. CE in pregnant women and in children under 5 years are however not recommended for CE. Chronic renal insufficiency is not, but liver insufficiency is an important issue in CE [3].

Although R-L shunts and PH are not a contraindication for CE anymore, we did not administer CEA in patients with R-L shunts or Eisenmenger syndrome. Whenever a suspicion occurred on a shunt, prior to CEA administration, bubble test was done with agitated saline.

The updated focused guidelines in 2014 for contrast use about AE or side effects denounced the risk of iv. commercial contrast agents in patients with small R-L shunts through a patent *foramen* ovale [16].

Perflutren gas, a component of Optison™, was eliminated through the lungs within 10 minutes after administration, but the interaction of Optison™ and other drugs were not studied and reported [3]. That is why we monitored patients for oxygen saturation during rest and stress CE, but AE never occurred. Wever-Pinzon et al. [6] published a study on 1,513 patients with PH who had received CE and were under control for 24 hours after the administration, but no respiratory decompensation, hypotension, arrhythmias, syncope, convulsions, anaphylactic reactions, or death was registered among them.

The preparation and the administration of CEA is an important part of the imaging. The administered doses of CEA in our study were not specified by any protocol. The injected doses of Optison™ were sufficient to opacify the LV cavity and endocardial border for several minutes in all cases of resting and SE. No patients received a total of 5.7 mL of CEA which is the highest dose proposed by the manufacturer [3].

The first indication for CEA according to the ASE guidelines was that it can "be used for improved endocardial visualization (ie., when two contiguous endocardial segments of the LV are not observed or to improve Doppler evaluations if the initial spectral signals are inadequate)" [4].

Today, inadequate segment visualisation is a first class recommendation, even one segment of the LV is not visualised [17].

The latest guideline for chronic coronary syndrome, pointed out that this imaging modality with CEA should precede cardiac magnetic resonance [18].

CE can accurately detect LV regional wall motion disturbances, even in technically challenging and obese patients [19]. Wall motion and MP analysis improved coronary artery disease (CAD) detection during SE with this imaging modality.

Wall motion analysis and MP defect detection were attempted in our patients not only with dobutamine or exercise SE, but PM SE as well, where an accelerated contrast SE was conducted in 25 of our patients, which is, according to our knowledge, the first group of patients with this kind of imaging modality.

In 2014, the contraindication was removed for the use of CEA in patients with recent acute coronary syndrome (ACS) or clinically unstable IHD [13]. Optison™ may also be used in ACS, what was presented in Galiuto et al. [20] paper.

Most resting and SE studies were performed with this imaging modality to evaluate LV endocardial border delineation for regional and segmental wall motion analysis and accurate measurement of the LV volumes and function [21].

The quantitative assessment of the EF of the LV is an important parameter, and CE measurements can provide similar values as cardiac magnetic resonance which is a "golden standard". It is well known that LV volumes obtained by CE are generally larger than by native echocardiography. CE can reduce interobserver variability [21, 22].

Our big concern was the LV apex visualisation on native echocardiography, what was the subject of our earlier research [12]. Apexes are often incompletely visualised, or trabeculations of the apical region can make the examination difficult [23].

It is clinically important to identify otherwise unrecognised thrombus in the apex of the LV. CE can improve the interpretation not only for the presence, but for the absence of an apical thrombus, because anticoagulation therapy will be introduced to prevent embolic event if the thrombus is detected, otherwise patients would be restricted from the unnecessary anticoagulation therapy if thrombus was excluded. Guidelines are still non uniform for the treatment of patients with parietal thrombi. With CE, the shape, the size and the embologenity of the thrombi can be more accurately assessed then with native echocardiography. Preventive checkups with CE would be necessary in patients prone to develop thrombi with large hypocontractile LV, or with an akinetic segment or aneurysms of the LV [9]. CE should be an integral part of the individualized

follow up and monitoring of anticoagulation therapy for registered thrombi in the heart chambers.

Cardiac masses in all heart chambers are an indication for CEA use, not only to determine the presence of the mass, but the vascularisation with perfusion imaging to determine the etiology of the questionable formation. Hyperenhancement of the mass would raise suspicion on its malign etiology [24].

In routine use of CE in patients with anterior MI, thrombi were reported in more than 20%, when there was even no suspicion at all with native echocardiography [25].

For the left appendage thrombus detection we performed transesophageal echocardiography (TEE) with CE in four of our patients.

We experienced the advantage of the CE in patients with suspected aortic dissection, since the diagnoses of aortic dissection by using CE were excluded three times and in one patient the dissection was confirmed.

There were a large number of patients in our investigated group with arrhythmias or PM, resinchronisation therapy, or cardioverter defibrilators, with valvular but also with congenital heart diseases.

The CE should not be withheld on the bases of any diagnoses or comorbidity [1] and may reduce health care cost because Optison™ helped define abnormalities that required appropriate hospitalization for further management [26].

During SE, CE was an option not only for IHD but for valve disesase for better evaluation of the highest velocity in mild stenotic lesions. Regional wall motion disturbances were registered with CE in rest and SE. The accuracy of CE was not compared to noncontrast study results in our patients, but according to the published papers of other investigators, there is a significantly higher accuracy in SE with CE for the detection of CAD, especially if they are done as multiparametric SE, not only for endocardial enhancement and wall motion analysis, but for coronary flow registration and MP and viability assessment as well [11, 27]. CE can improve interobserver agreement for wall motion analysis [28]. MP is a promising indication in CE, which can give us diagnostic and prognostic information. The use of ECA improved not only image quality, but the reader confidence of interpretation as well [29]. Comprehensive evaluation in IHD is the optimal approach for noninvasive assessment of the coronary artery lesions [30]. Our great concern was the interaction of the CEA with other therapy and medications. Some of the patients were on anticoagulation therapy and had chronic kidney disease (CKD) or obstructive pulmonary diseases. Interactions with medications and Optison™ were not investigated or referred to in the previous studies. Our patients were on a large variety of medications and had different diagnoses and that is important and encouraging for the routine clinical use of the CEA.

In 2007, after 4 deaths and several severe cardiopulmonary reactions occurred after the use of Definity™ and Optison™, the FDA issued a black box warning, which turned out to be unjustified [31], but added new contraindication for patients with PH and unstable chronic pulmonary disease and required a 30 minutes post-procedure monitoring period after the use of ECA.

We decided to follow these instructions and precautions, although the warnings were later withdrawn. The 30 minutes follow up time after the administration of Optison™ was conducted while heart rate, blood pressure, oxygen saturation and body temperature monitoring was completed. Systolic and diastolic blood pressure was slightly lower in patients after the administration of Optison™. Heart rate increased after the application of the CEA but it was clinically irrelevant.

Slightly higher temperature was registered in patients, in average, after the administration of Optison™, but the values were never above 37 °C. We have to point out that patients with a suspicion of infectious diseases or fever would not be given CEA. The minor change of the body temperature is clinically irrelevant after the administration of CEA. Patients with infectious diseases should avoid Optison™, but such observation was not a subject of previous reports although the manufacturer mentioned it [3].

The follow up was not continued after this monitoring period, thus, it is possible that some events were missed. Previous reports found that serious AEs to CEAs (allergic or anaphylactoid reactions) occurred early after administration, usually within 30 minutes [3], so it is unlikely that significant later AEs were missed.

There have been several published articles and reviews arguing both the safety and efficacy of CEAs in several large variety of patients, with PH followed up for 24 hours after the administration of CEA but no respiratory decompensation, hypotension, arrhythmias, syncope, convulsions, anaphylactic reactions, or death were registered among these patients [6, 15].

We think that patients taking cardiovascular medication and/or been undergoing SE with or without pharmacological stressor are a challenging group to follow up the AEs for CEAs, since the interaction of all these medications and CEA are difficult to analyse even in randomised circumstances.

For safety reasons, other authors followed up patients for 30 minutes after dobutamine or exercise stress testing with CEA. Among the reported symptoms, there were chest pain, arrhythmias such as premature atrial contractions, premature ventricular contractions, nonsustained ventricular tachycardia, hypertension, tachycardia, electrocardiographic changes, dyspnea, nausea, vomiting, tremor, and dizziness. None of these AEs were attributed to Optison™. There were no anaphylactoid reactions or deaths during or after studies conducted [8, 34].

Publishing on the safety and improved efficacy of CEAs in the retrospective studies [32] showed that propensity-matched patients who underwent a CE were 24% less likely to die within 1 day than patients who did not receive an CEA. Similar result was obtained in another study where 2,518 patients who received CEA had less overall one day mortality than patients who did not receive CEA [7].

Several authors also noted the safety of these agents in SE as well as the lack of AEs in long-term follow-up [31, 32].

In a retrospective study including 5,956 patients who received CE and were monitored for AEs, back pain and rash were registered in only 0.27% of the observed patients, but

there were no cases of serious anaphylaxis or death within 30 minutes of the contrast administration [8].

In prospective safety study of Optison™ [33] which included 203 patients, 37% of the patients had dilated CMP with diminished LV EF (20%–40%). There were no changes in the monitored vital signs. Patients were also followed up for AEs, but none of them were noted. Similar results were obtained in our study in patients with dilated CMP (Figure 4).

There is a trend toward improvement in outcomes when such patients undergo contrast-enhanced rather than unenhanced echocardiography [26, 38].

Extracardiac application of a CEA, for carotid, femoral, aortic endografts, peripheral perfusion is also recommanded. Among others, emerging applications are molecular imaging, targeted drugs-gene therapy and thrombolysis [1, 2].

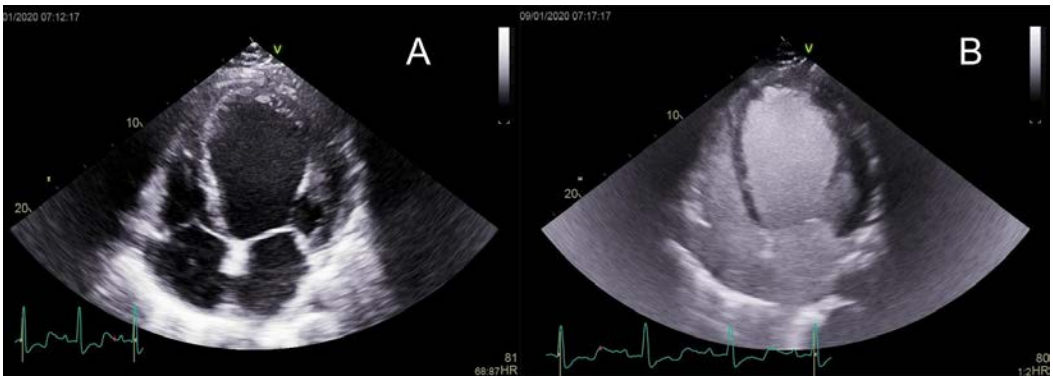

Fig. 4 – Dilated cardiomyopathy is shown using contrast echocardiography.

A prospective randomized trial showed that an abnormal MP with CE was more often observed than in conventional SE, and more frequently resulted in revascularization [29]. Significantly more cases of ischemia were diagnosed with MP CE and detected a greater ischemic burden than in the case of wall motion analysis in patients undergoing native SE [34].

Since 2012, the FDA has removed the need for monitoring of patients with PH, unstable chronic pulmonary diseases and stress testing [32]. In October 2016 shunt contraindications were removed [35]; since then this modality in patients with PH and shunts have not been a contraindication any more. Accordingly, the monitoring of vital signs can be practiced only in selected cases of patients with PH or R-L shunts [1, 2].

CE is a minimally invasive technique for perfusion analysis [36], by which sometimes other diagnostic modality can be avoided. When comparing noninvasive diagnostic methods in a study conducted by Senior et al. [37], CE demonstrated superior sensitivity but lower specificity for the detection of CAD as compared to scintigraphy, when results were confirmed by coronary angiography.

The CE can be and should be routinely used, not only in clinics and hospitals, but in every local outpatient office with an appropriate echocardiographic facility, since it is a safe and cost effective diagnostic modality.

Limitations of the study

The main limitation of this study was the sample size.

Conclusion

Contrast echocardiography with Optison™ as a CEA, is a very safe, noninvasive diagnostic modality, useful in a large variety of clinical settings, in patients being on medical treatment and undergoing resting and SE in the routine everyday clinical practice. It is important to check all the issues before performing CE concerning the patient selection which should be individualized, to exclude persons with allergy and to strictly follow the administration methodology. Vital parameter changes after Optison™ administration were clinically irrelevant.

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