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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 purpose of this study was to present the initial clinical experience of the use of CEA in Institute for CVD of Vojvodina, Serbia and prospectively determine the safety of Optison (GE Healthcare, Princeton, NJ).

**Methods.** A total of 357 patients (PTS) were referred for resting or stress echocardiographic examinations, with an approved indication for CEA administration. The median age was 63.3 years (range, 21–92 years), 62% were men. Most of the PTS (77.31%) had some form of ischemic heart diseases. Hypertension has been the most frequent risk factor (77.03%), but 57 PTS had diabetes mellitus and 33 PTS chronic kidney disease as comorbidity. Most PTS (90.5%) were on beta blocker therapy, 83.5% of them on ACEi/angiotensin blockers. Majority of the PTS received single (80.3%) or dual (49.5%) antiaggregation therapy, 74 (26.3%), of them were on AKTH, 55.1% of the PTS were taking diuretics. The global EF was preserved in 39.85% of them, the majority had LV impairment, 136 PTS of them, with an EF less than 50%. PTS were followed up for 30 minutes for side effects (SE). In 118 PTS, vital signs (heart rate, oxygen saturation, body temperature, systolic and diastolic blood pressure) were measured before and 30 minutes later after CEA administration.

**Results.** The administration of CEA-Optison was not associated with SE. Diastolic blood pressure drop was statistically significant (p=0.027) and the heart rate increased for 4.7 beat/min, which was statistically significant, too (p=0.028).

**Conclusion.** Vital signs changes were clinically non-relevant. CE is a safe noninvasive diagnostic modality for PTS undergoing rest and stress echocardiography.
Apstrakt

Uvod/Cilj. Kontrastna ehokardiografija (CE) je dijagnostička metoda koja podrazumeva aplikaciju kontrastnog medijuma (CEA) u perifernu venu za poboljšanje ehokardiografske slike.

Cilj je, da se prikaže inicijalno iskustvo upotrebe Optisona (GE Healthcare, Princeton, NJ) kao CEA u Institutu za kardiovaskularne bolesti Vojvodine, u Sremskoj Kamenici, u Srbiji kao i prospektivno praćenje pojave eventualnih nuzefekata.

Metodologija. Procedura CE je urađena kod 357 pacijenata (PAC) kod kojih je postavljena indikacija za davanje CEA u miru i/ili stresehokardiografiji (srednje godine starosti 63,3 godina, od 21 do 92 godine) 62% ispitanika je muškog pola.

Ispitanici su imali različite kliničke dijagnoze, ali najveći broj PAC (77,31%) je imalo neku formu ishemijske bolesti srca. Hipertenzija je najčešći riziko faktor kod ispitanika (77.03%), a od komorbiditeta šećerna bolest je bila prisutna kod 57 PAC, a 33 PAC je imalo hroničnu bubrežnu insuficijenciju.

Većina PAC je uzimalo beta blokatore (90,5%), a 83,5% je koristilo ACEi, ili angiotenzin blokatore. 80.3% je dobijalo mono, a (49.5%) dvojnu antiagregacionu terapiju dok je 74 pacijenta (26.3%) dobijalo antikoagulantnu terapiju. Diuretike ih je koristilo 55,1% PAC.

Sa očuvanom globalnom ejekcionim frakcijom (EF) leve komore (LK) ih je bilo 39,85%, a većinu ih je imala smanjenu EF LK, tj. manju od 50%, njih 136. Nakon davanja Optisona, PAC su praćeni još 30 minuta zbog pojave neželjenih efekata. Kod njih 118 PAC je pre i 30 minuta nakon davanja CEA beleženi vitalni parametri (frekvenca srca, saturacija krvi kiseonikom, temperatura tela, sistolni i dijastolni krvni pritisak).

Rezultati. Nuspojave nisu beležene kod naših ispitanika. Nakon davanja Optisona, promena dijastolnog krvnog pritiska je pokazala statističku signifikantnost (p=0.027) kao i ubrzanje pulsa u proseku za 4.7/min, što je takođe statistički značajan porast (p=0.028).
**Zaključak.** Promene praćenih vitalnih parametara nemaju klinički značaj. CE je sigurna neinvazivna ehokardiografska metoda u miru i stresehokardiografiji za široki spektar bolesnika.

**Ključne reči:** transpulmonalna kontrastna ehokardiografija, kardiološka dijagnoza, ehokardiografija, kontrastno sredstvo

**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 while 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. The initial use of the CE were technically difficult or uninterpretable echo images. 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 echo.

Studies demonstrated the efficacy and safety of CEA improving the diagnostic utility of both rest and stress echocardiography.

For transpulmonary ECA the indication in clinical cardiology is the enhancement of the LV endocardial border, accurate and repeatable measurements of volumes, global and regional LV function, especially in patients (PTS) who are candidates for chemotherapy, to establish the diagnosis of apical hypertrophy, LV thrombus or other intracardiac mass evaluation, non compaction cardiomyopathy (CMP), to assess myocardial perfusion (MP) in rest and in multiparametric stress echocardiographic studies to assess coronary flow reserve (CFR) and/or viability, too.

The contraindications in nonpregnant adults are allergic reactions to the components of the ECA, precaution is recommended with pulmonary hypertension (PH) and right to left (R-L) shunts. Side effects are rare and usually not serious.
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 growing1,2. The purpose of this paper was to present the initial experience and the safety of Optison (GE Healthcare, Princeton, NJ) as an ECA in routine medical practice in the Institute for CVDV, Sremska Kamenica, Serbia.

Methods
This was an observational prospective study from March 2017 to November 2019 at the Institute for cardiovascular diseases of Vojvodina in Sremska Kamenica, Serbia. During this period a total of 357 PTS with technically difficult echocardiographic studies underwent CE study. Informed consent was obtained from all PTS. Data collected from each subject included demographics, history, and information on allergies. PTS with known hypersensitivity to perflutren, blood, blood products, or albumin was not included in the study and neither were individuals with previous history of any food allergies. The presence of any infection or fever were also non including criteria. Clinical diagnoses, risk factors and comorbidities, medications of the PTS, 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 the CE.

Preparation and administration of the CEA required attention to the storage, preparation and application. The glass vials of the CEA were stored in a refrigerator with a temperature between 2-8 °C. The preparation protocol and the administration method followed the instruction given by the manufacturer3. 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 exceeds a room temperature. PTS would have been prepared and inserted with IV canulla with at least 20 gauge with the 3 way stopkok into the peripheral vein-usually into the right arm. The rate of the IV bolus did not exceed 1ml per second, flushed with 10ml saline. The administered doses of CEA in our study were not specified in most of the PTS the bolous injection of the CEA was 0,3 or 0,4 ml intravenously followed by a 10 ml slow saline flush. The maximum total dose did not exceed 1,5mL, whenever the image was acceptable, the dose of the Optison would not have been repeated, except in stress echo studies where usually at least two bolous doses would have been 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 stress echoes.

Statistical analysis
Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as frequencies in percentages. Statistical significance was calculated by Student’s t-test and p < 0.05 was considered statistically significant.

| Variable                      | N  | %    |
|-------------------------------|----|------|
| **Gender (total number)**     |    |      |
| Male                          | 244| 68.3 |
| Female                        | 113| 31.7 |
| Age (year), x ± SD            | 63.28 ± 11.40 |
| BSA, x ± SD                   | 1.99 ± 0.22 |
| **Clinical diagnoses (total number)** | 357 |      |
| Ischemic heart diseases       | 276| 77.31|
| Rhythm disturbances           | 101| 28.29|
| PTS with PACEmakers, ICD or CRT | 21 | 5.88 |
| Cardiomyopathies              | 85 | 23.81|
| Congenital and valvular heart diseases | 96 | 26.89 |
|----------------------------------------|----|-------|
| **Risk factors and comorbidities (total number)** | 357 | |
| Hyperension                            | 275 | 77.03 |
| Diabetes mellitus                      | 59  | 16.53 |
| Chronic kidney disease                 | 33  | 9.24  |
| Obstructive lung diseases              | 17  | 4.76  |
| **Medications of the PTS recived CE (total number)** | 285 | |
| ACEinhibitors/AT blockers               | 238 | 83.5  |
| Betablockers                           | 258 | 90.5  |
| Statins                                | 210 | 73.7  |
| Dual Antiaggregation th                 | 141 | 49.5  |
| Aspirin                                | 229 | 80.3  |
| Anticoagulant therapy (AKTH)            | 74  | 26.3  |
| Diuretics                              | 157 | 55.1  |
| Ca antagonists                         | 41  | 14.4  |
| **EFLV (total number)**                | 332 | |
| <40 %                                  | 96  | 28.9  |
| 40%-50 %                               | 104 | 31.3  |
| >50 %                                  | 132 | 39.8  |
| **Indications for TPKE (total number)** | 357 | |
| 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 (TEE) | 4  | 1.12  |
| Stresreh (Dobutamin, adenozin and dobutamin, pace maker (PM) | 152 | 42.58 |
| stresreh, exercise stresreho)          |     |       |

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

PTS were referred for routine resting or stress echocardiographic examinations, with an approved indication for CEA administration, fulfilled at least one of the indications listed in Tab. 1.

Most of the PTS (77.31%) had some form of ischemic heart diseases (IHD). Rhythm disturbances, CMPs, congenital and valvular heart diseases were also represented among the investigated PTS. In 3 of them since CE was introduced, apical hypertrophic CMP was newly diagnosed.

PTS were with a large number of comorbidities. Hypertension has been the most frequent risk factor, but there were 57 PTS with diabetes mellitus and 33 PTS with chronic kidney disease (CKD) as comorbidity. Most PTS (90.5%) were on beta blocker therapy, while 83.5% on ACEi/angiotensin blockers. Majority of the PTS received Aspirin or dual antiaggregation therapy, 74 of them were even on AKTH, 55.1% of the PTS were on diuretics.

The global EF was preserved only in 39.85% of them, the majority had LV impairment, 136 PTS of them, with an EF less than 50%.

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 them when CE was introduced, apical hypertrophic CMP was newly diagnosed.

One patient was diagnosed with CE successfully with LV diverticulum.

Most of the stress echocardiographic studies were indicated for PTS with previous history of IHD and chest pain. Exercise, medicament and PM stress echocardiography were performed with Optison. There were dobutamin and adenosine stress echocardiographies also. There were 2CE exercise stres echocardiographies for valve diseases-mild aortic stenoses- and for congenital heart diseases, two PTS had corrected transposition of the great arteries. In 4 PTS the indication for Optison administration was the left auricle exploration before electroconversion. In PTS with suspected aortic dissection 3 times were excluded the diagnosis with CE, in one patient the dissection was confirmed with CE.
PTS 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 (SA) were present in our group. No allergic or anaphylactoid reactions occurred.

In 118 PTS, vital signs (heart rate, oxygen saturation, body temperature, systolic and diastolic blood pressure) were measured before and followed up after 30 minutes after the administration of the CEA—what is shown in Tab. 2. No AEs were reported.

PTS on stress echo were checked up during baseline echo and 30 min after the rest stage ends.

Table 2

Vital parameters before and after the administration of ECA in 118 PTS

| Variable                      | Before (x ± SD) | After (x ± 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|

\( \bar{x} \) – mean value; SD – standard deviation

The average systolic and diastolic blood pressure was lower after the administration of Optison. The diastolic drop was even of statistical significance \((p=0.027)\) and the heart rate increased for 4.7 beat/min on average, which was statistically significant, too \((p=0.028)\), but the changes were clinically non-relevant.

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

**Discussion**

Today, there are three new, commercially available 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 FDA for the indication of left ventricle opacification (LVO) in adults\(^{12}\).
The “Levovist” produced by Schering AG (Berlin, Germany) in 1985 was the first commercially available ECA\textsuperscript{10}. Initially, the idea to use it were PTS with poor acoustic window or uninterpretable images\textsuperscript{4,5}.

From the time being, Optison is the only available CEA in Serbia. Its routine administration started at the Institute for cardiovascular diseases of Vojvodina, Sremska Kamenica in 2017, after a project was accepted and approved by the Local government\textsuperscript{12}. The regulatory documents and the permission was obtained from the Republic Ministry of health for this method.

Optison is a sterile, non-pyrogenic suspension of microspheres or microbubbles-filled with perflutren gas in albumin shell-that are small and stable enough to pass the pulmonary circulation during the ultrasound imaging procedures. The microbubbles create an echogenic contrast effect in the blood, so this imaging modality is called transpulmonary CE\textsuperscript{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 and by the American Society of Echocardiography\textsuperscript{1,2,9,11}.

A review on the safety of ECA compared to the other commonly used radiology contrast agents pronounced them safe, reliable and radiation-free diagnostic modality\textsuperscript{7,8}.

To perform CE- the ultimate must have is-beside the CEA, an ultrasound machine which is equipped with adequate- low MI contrast software. The MI stands for the measure of the power generated by the transducer during the echocardiographic examination.

SA of CEAs are rare and usually not serious, but the administration can be associated with flushing, headache, nausea, vomiting, dyspnoea, 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 rare\textsuperscript{3}.

The incidence of an anaphylactoid reaction from ECA exposure has been estimated at about one in 15,000\textsuperscript{13,14,15}, so our sample size could not be able to detect such rare events. According the recommendations, both “physicians and sonographers 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\textsuperscript{1,2}.

In our PTS, systematic preprocedural detailed history was taken with special care of those allergic to proteins (blood products, food or other medications). With positive history data
or even a suspicion on a possible allergy or elevated temperature, the PTS would not have been 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, since 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 PTS were indicated in accordance with the latest recommendations\textsuperscript{1,2}. More than two thirds of them had low EFLV, some of them had acute IHD and congestive heart failure, but all of them tolerated Optison well. In other reports\textsuperscript{15,16}, also noted a low serious SE rate of 0.01\% in those PTS that received ECAs.

PTS included in our study represent those individuals 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\textsuperscript{3}.

Even R-L shunts and pulmonary hypertension (PH) are not a contraindication for CE anymore, we have not administered it in PTS with R-L shunts or Eisenmengen 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 by the ASE denote the risk of i.v. commercial contrast agents in PTS with small R-L shunts through a patent foramen ovale\textsuperscript{17}.

Perfluorren gas—a component of the Optison CEA is eliminated through the lungs within 10 min after administration, but the interaction of Optison and other drugs have not been studied and reported\textsuperscript{3}. That’s why we monitored PTS for oxigen saturation during rest and stress CE, but AE did never occur. Wever-Pinzon et al.\textsuperscript{6} published a study on 1513 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 the 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 stress echocardiographies. No PTS received a total of 5.7ml/ which is the highest dose proposed by the manufacturer. The first indication for CEA according to the ASE guidelines were that it can “be used for improved endocardial visualization (i.e., when two contiguous endocardial segments of the LV are not observed or to improve Doppler evaluations if the initial spectral signals are inadequate)”

Today, inadequate segment visualisation is a first class recommendation even one segment of the LV is not visualised. The latest guideline for chronic coronary syndrome, pointed out, that this imaging modality with CEA should preceed cardiac magnetic resonance. CE can detect accurately LV regional wall motion disturbances, even in technically challenging and obese PTS. Wall motion and myocardial perfusion (MP) analysis improved coronary artery disease (CAD) detection during stress echo with this imaging modality.

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

In 2014, the contraindication was removed for the use of CEA in PTS with recent acute coronary syndrome (ACS) or clinically unstable IHD. Optison may be used in ACS also, what was presented in Galiutos paper. Most resting and stress echocardiographic 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. The quantitative assessment of the EF of the LV is an important parameter, and CE measurements can obtain 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. Our big concern was the LV apex visualisation on native echocardiography, what was the subject of the project. Often, apexes are incompletely visualised, or trabeculations of the apical region can make difficult the examination.
To identify otherwise unrecognised thrombus in the apex of the LV is clinically important. CE can improve the interpretation not only for the presence, but for the absence of an apical thrombus, because AKTH will be introduced to prevent embolic event if the thrombus is detected, otherwise PTS would have been restricted from the unnecessary AKTH if it is excluded. Guidelines are still non uniform for the treatment of PTS with parietal thrombuses. With CE, the shape, the size and the embologenity of the thrombi can be more accurately assessed then with native echo. Preventive checkups with CE would be necessary in PTS prone to develop thrombi with large hypocontractile LV, or with an akinetic segment or aneurysms of the LV. CE should be an integral part of the individualized follow up and monitoring of AKTH for registered thrombi in the heart chambers. Figure 1. showing CE in a patient with large parietal thrombus—which is shown as avascular-black- formation at the LV apex, on transthoracic four chamber view.

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 the malign etiology of it. In routine use of CE in PTS with anterior MI, thrombi were reported in more than 20%, when there was even no suspicion at all with native echocardiography.

For the left appendage thrombus detection we performed TEE with CE in four of our PTS. We experienced the advantage of the CE in PTS with suspected aortic dissection, since 3 times were excluded the diagnosis with CE, in one patient the dissection was confirmed with CE.

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

Among others, there were a large number of PTS in our investigated group with arrhythmias or PM, resynchronization therapy, or cardioverter defibrilators, with valvular but also congenital heart diseases, too.

The CE should not have been withheld on the bases of any diagnoses or comorbidity and may reduce health care cost because Optison helped define abnormalities that required appropriate hospitalization for further management.
The first patient was diagnosed successfully with the LV diverticulum (Figure 3) in our Institute with the use of CE. It was done in dextrocardiac PTS and with corrected transposition of the great arteries but none of them had a R-L shunt. During stress echocardiography CE was an option not only for IHD but for valve disease for better evaluation of the highest velocity in mild stenotic lesions. Regional wall motion disturbances were registered with CE in rest and stress. The accuracy of CE was not compared to noncontrast study’s results in our PTS, but according to the published papers of other investigators, there is a significantly higher accuracy in stress with CE for the detection of CAD, especially if they are done as multiparametric stress echocardiographies not only for endocardial enhancement and wall motion analysis, but for coronary flow registration and MP and viability assessment, too. CE can improve interobserver agreement for wall motion analysis. 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. Comprehensive evaluation in IHD is the optimal approach for noninvasive assessment of the coronary artery lesions.

Our great concern was the interaction of the CEA with other therapy and medications. Some of them were on AKTH and had CKD or obstructive pulmonary diseases. Interactions with medications and Optison was not investigated or referred in studies. Our study group PTS were on a large variety of medications and had different diagnoses-what is important and encouraging for the routine clinical use of 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 was unjustified, but added new contraindication for PTS with PH and unstable chronic pulmonary disease and required a 30 min post-procedure monitoring period after the use of ECA.

We decided to follow these instructions and precautions, even the warnings were later with droll. The 30 min follow up time after the administration of the Optison while HR, blood pressure, oxigen saturation and body temperature monitoring was completed. Systolic and diastolic blood pressure was slightly lower in PTS after the administration of Optison. HR increased after the application of the CEA but it was clinically irrelevant. Slightly higher temperature was registered in PTS in average after the administration of Optison, but the values were never above 37C. We have to point out, that PTS with a
suspicion of infectious diseases or fever would have not been given CEA. The minor change of the body temperature is clinically irrelevant after the administration of CEA. PTS with infectious diseases should avoid Optison, but such observation was not a subject of previous reports even the manufacturer mentioned it³.

The follow up was not continued after this monitoring period, thus, it is possible that some events were missed. Previous reports have found that serious AEs to ECAs (allergic or anaphylactoid reactions) occur early after administration, usually within 30 min⁴, so it is unlikely that significant later AE were missed.

There have been several published articles and reviews arguing both the safety and efficacy of ECAs in several large variety of PTS, with PH followed up for 24h after the administration of CEA but no respiratory decompensation, hypotension, arrhythmias, syncope, convulsions, anaphylactic reactions, or death was registered among these PTS⁶,¹⁶. We think, that PTS taking cardiovascular medication and/or been undergoing stress echocardiography 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.

Other authors for safety reasons followed up PTS 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 the study⁸,³⁴.

Publishing on the safety and improved efficacy of ECAs in a retrospective studies³², propensity-matched PTS who underwent a CE were 24% less likely to die within 1 day than were PTS who did not receive an ECA, so as it was in the other study, where 2518 PTS were analysed who received KE, had less overall one day mortality then PTS did not receive ECA⁷.

Several authors also noted the safety of these agents in stress echocardiograms as well as the lack of AE in long-term follow-up³¹,³².

In a study which performed a retrospective analysis on 5956 PTS who received CE and were monitored for AE, where back pain and rash were registered in only 0.27% of the
observed PTS, there were no cases of serious anaphylaxis or death within 30 minutes of the contrast administration\textsuperscript{8}.

Prospective safety study of Optison was published\textsuperscript{33} which included 203 patients, and 37\% of the PTS had dilated CMP—with diminished LVEF between 20\%–40\%—so it was similar as in our group and there were no changes in the monitored vital signs. The PTS were also followed up for AEs, but none of them were noted, as in our group, there were also PTS with dilated CMP (Figure 4.).

A prospective randomized trial showed that an abnormal MP with CE was more often observed than in conventional stress echo, and resulted in revascularization more frequently\textsuperscript{30}. Significantly more cases of ischemia were diagnosed with MP CE and detected a greater ischemic burden than did with wall motion analysis PTS undergoing native stress echocardiography\textsuperscript{34}.

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

CE is a minimally invasive technique for perfusion analysis\textsuperscript{36}, by which sometimes other diagnostic modality can be avoided. When comparing noninvasive diagnostic methods in a study conducted by Senior et al.\textsuperscript{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 costeffective diagnostic modality.

There is a trend toward improvement in outcomes when such PTS undergo contrast-enhanced rather than unenhanced echocardiography\textsuperscript{38,39}.

Extracardiac application of the CEA, for carotid, femoral, aortic endografts, peripheral perfusion is also recommended. Among others, emerging applications are molecular imaging, targeted drugs–gene therapy and thrombolysis\textsuperscript{1,2}.

\textbf{Conclusion}
From the initial experience with Optison as a CEA, the administration was not associated with SE so it can be concluded that this is a very safe, noninvasive diagnostic modality, useful in a large variety of clinical settings, in PTS being on medical treatment undergoing resting and stress echocardiography in the routine everyday clinical practice, so CE should be widespread in routine use. It is important to check all the issues before performing CE concerning the patient selection which should be individualised-to exclude persons with allergy and to strictly follow the administration methodology. Vital parameter differences after Optison administration, were clinically irrelevant.

Limitations. The main limitation of this study was the study size.

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Acute coronary syndrome (ACS)

anticoagulant therapy (AKTH)

American Society of Echocardiography (ASE)

cardiomyopathy (CMP)

chronic kidney disease (CKD)

Contrast echocardiography (CE)

coronary artery disease (CAD)

coronary flow reserve (CFR)

ejection fraction (EF)

Heart rate (HR)

ischemic heart diseases (IHD)

left ventricle (LV)

left ventricle opacification (LVO)

mechanical index (MI)

myocardial perfusion (MP)

pace maker (PM)
patients (PTS)
pulmonary hypertension (PH)
right to left (R-L)
serious adverse event (SAE)
side effect (SE)
Transoesophageal echocardiography (TEE)
transpulmonary contrast echocardiographic agent (CEA)
US Food and Drug Administration (FDA)
## TABLES IN METHODOLOGY

Table 1: Clinical characteristics and indication for CEA

| Variable                        | N   | %   |
|---------------------------------|-----|-----|
| Gender (total number)           | 357 |     |
| Male                            | 244 | 68.3|
| Female                          | 113 | 31.7|
| Age (year), x ± SD              | 63.28 ± 11.40 |     |
| BSA, x ± SD                     | 1.99 ± |     |
## Clinical diagnoses (total number) 357

| Diagnosis                                      | Number | Percentage |
|-----------------------------------------------|--------|------------|
| Ischemic heart diseases                       | 276    | 77.31      |
| Rhythm disturbances                           | 101    | 28.29      |
| PTS with PACEmakers, ICD or CRT               | 21     | 5.88       |
| Cardiomyopathies                              | 85     | 23.81      |
| Congenital and valvular heart diseases         | 96     | 26.89      |

## Risc factors and comorbidities (total number) 357

| Condition                              | Number | Percentage |
|----------------------------------------|--------|------------|
| Hyperension                            | 275    | 77.03      |
| Diabetes mellitus                       | 59     | 16.53      |
| Chronic kidney disease                  | 33     | 9.24       |
| Obstructive lung diseases               | 17     | 4.76       |

## Medications of the PTS recived CE (total number) 285

| Medication                              | Number | Percentage |
|-----------------------------------------|--------|------------|
| ACEinhibitors/AT blockers                | 238    | 83.5       |
| Beta blockers                            | 258    | 90.5       |
| Statins                                  | 210    | 73.7       |
| Dual Antiagregation th                   | 141    | 49.5       |
| Aspirin                                  | 229    | 80.3       |
| Anticoagulant therapy (AKTH)             | 74     | 26.3       |
| Diuretics                                | 157    | 55.1       |
| Ca antagonists                           | 41     | 14.4       |

## EFLV (total number) 332

| EFLV (%)                                | Number | Percentage |
|-----------------------------------------|--------|------------|
| <40 %                                    | 96     | 28.9       |
| 40%-50 %                                 | 104    | 31.3       |
| >50 %                                    | 132    | 39.8       |

## Indications for TPKE (total number) 357

| Indication                              | Number | Percentage |
|-----------------------------------------|--------|------------|
| 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 (TEE) 4 1.12
Stresseho (Dobutamin, adenosin and dobutamin, pace maker (PM) 152 42.58
stresseho, exercise stresseho)

Table 2

Vital parameters before and after the administration of ECA in 118 PTS

| Variable                        | Before              | After               | p     |
|---------------------------------|---------------------|---------------------|-------|
|                                 | (\(\bar{x}\) ± SD) | (\(\bar{x}\) ± SD) |       |
| 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 |

\(\bar{x}\) – mean value; SD – standard deviation

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