Keynote lecture

MITRAL REGURGITATION AND TAKOTSUBO: A DANGEROUS LIASON

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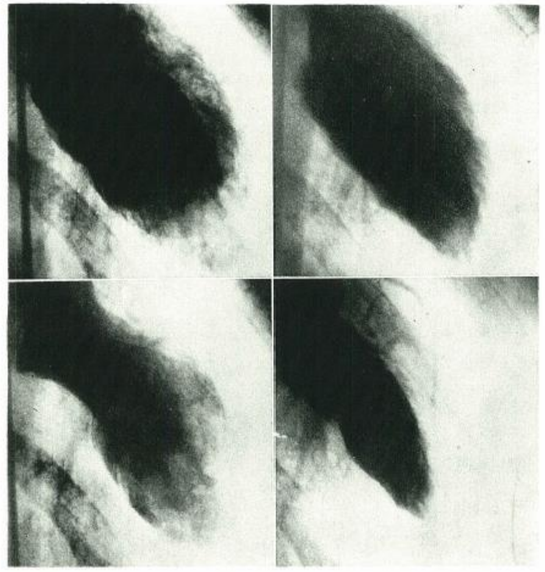
34 years since original description of Takotsubo Syndrome by Sato

Sato H, Tateishi H, Uchida T, Dote K, Ishihara M. Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. In: Kodama K, Haze K, Hori M, editors. Clinical aspect of myocardial injury: from ischemia to heart failure. Tokyo: Kagakuhyoronsha Publishing Co.; 1990. p. 56–64. (in Japanese)

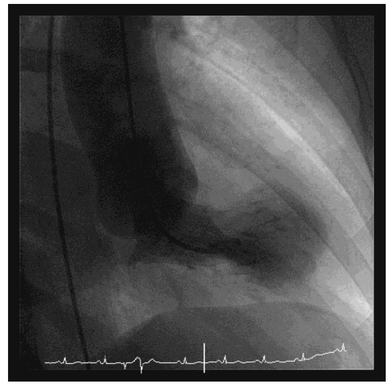


Prof. H. Sato (left)

Figure 2. The left ventriculography of Case 1 at admission (left) and a week later (right)
The left ventricle had a unique “Takotsubo shape” and it disappeared after a week.

Thanks to Birke Schneider

Why ‘Takotsubo’?
First described in Hiroshima, Japan 1990



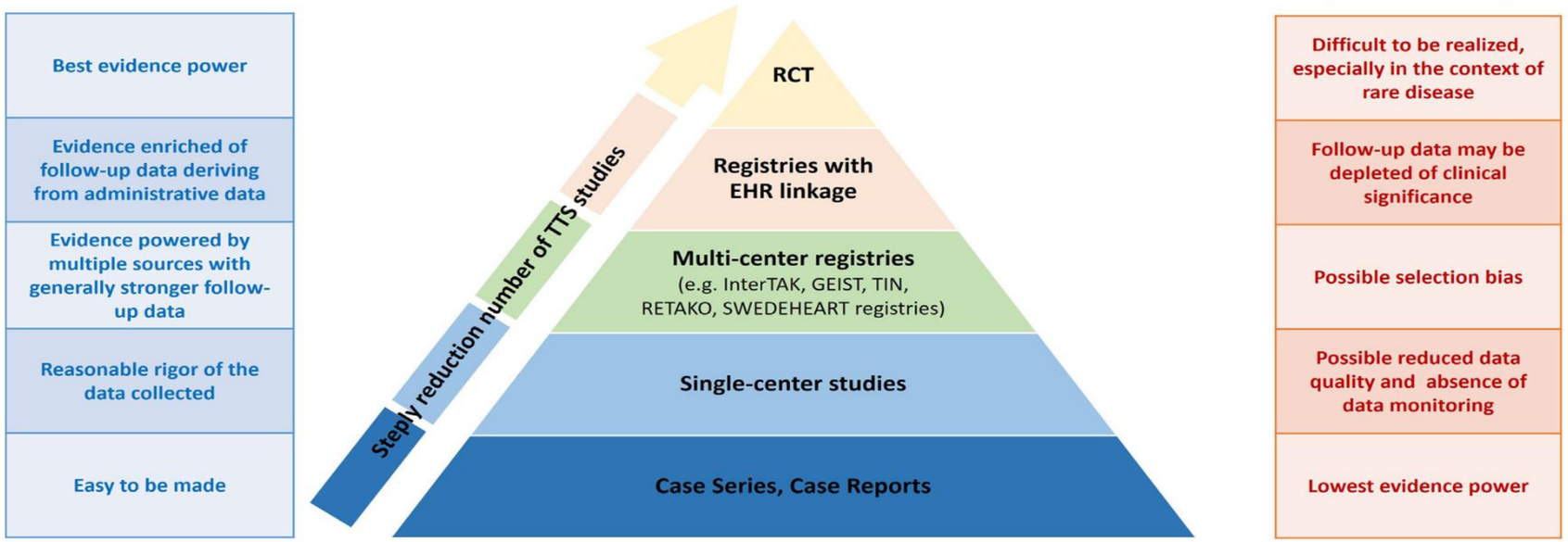
蛸壺

蛸 (tako) means octopus, the left-hand side of the character (虫) is the “insect/worm/snake/reptile/shellfish radical”; (肖) is originally composed of 小 “small” and 肉 “flesh,” so the character could be sourced to meaning: “small fleshy, reptile-like animal.”

壺 (tsubo) means “pot,” and may be combined, for example, with the character “tea” 茶 to form the word tea-urn in Japanese or teapot in Chinese (茶壺). Its lower, hollow cross-shaped part (亞) represents the bulging section of a pot, the upper part (士) represents the lid.

Evidence Pyramid in Takotsubo Syndrome

FIGURE 1 Evidence Pyramid in TTS With Strenghts and Weaknesses of Each Step



EHR = electronic health records; RCT = randomized clinical trial; TTS = Takotsubo syndrome.

Citro R, Bellino M, Silverio A JACC ADVANCES 2023

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2020) **21**, 1184–1207
doi:10.1093/ehjci/jeaa149
EACVI CONSENSUS DOCUMENT

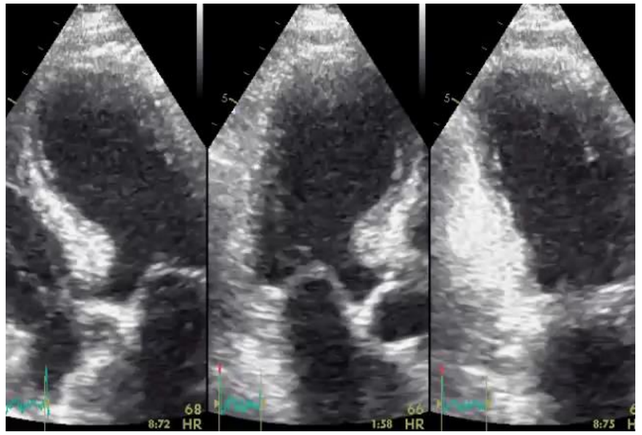
Multimodality imaging in takotsubo syndrome: a joint consensus document of the European Association of Cardiovascular Imaging (EACVI) and the Japanese Society of Echocardiography (JSE)

Rodolfo Citro (Chair)[1]*, Hiroyuki Okura (Co-Chair)[2], Jelena R. Ghadri[3], Chisato Izumi[4], Patrick Meimoun[5], Masaki Izumo[6], Dana Dawson[7], Shuichiro Kaji[8], Ingo Eitel[9,10], Nobuyuki Kagiyama[11], Yukari Kobayashi[12], Christian Templin[3], Victoria Delgado[13], Satoshi Nakatani[14], and Bogdan A. Popescu[15,16]

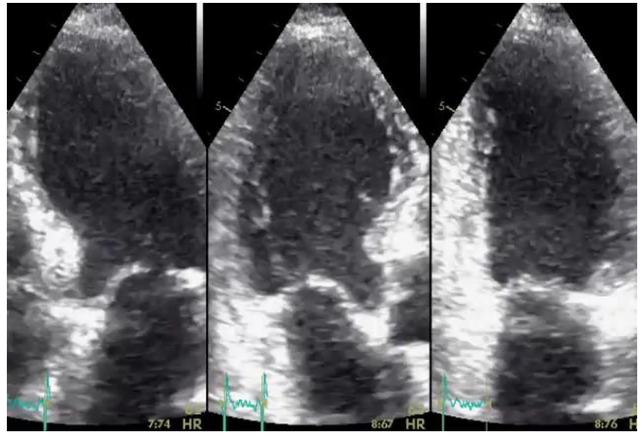
Dr. Hiroyuki Okura Dr. Rodolfo Citro

MMI in TTS diagnosis

POCUS for diagnostic suspect of TTS *#echofirst*



Acute phase



Post-acute phase

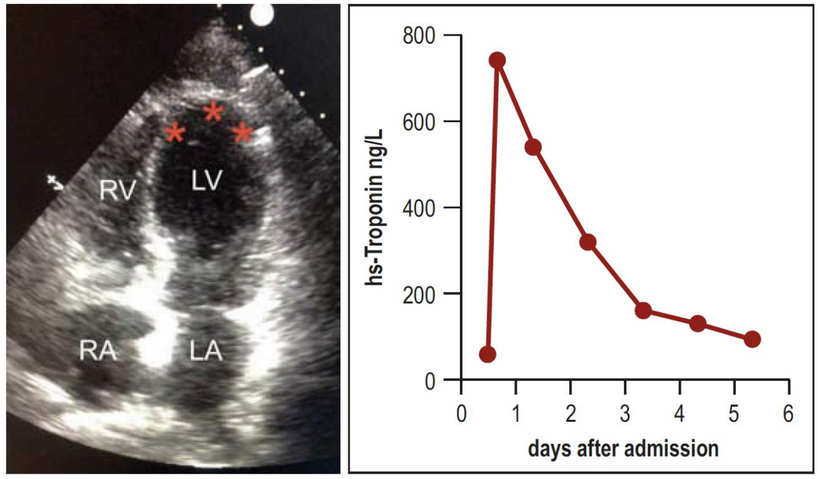
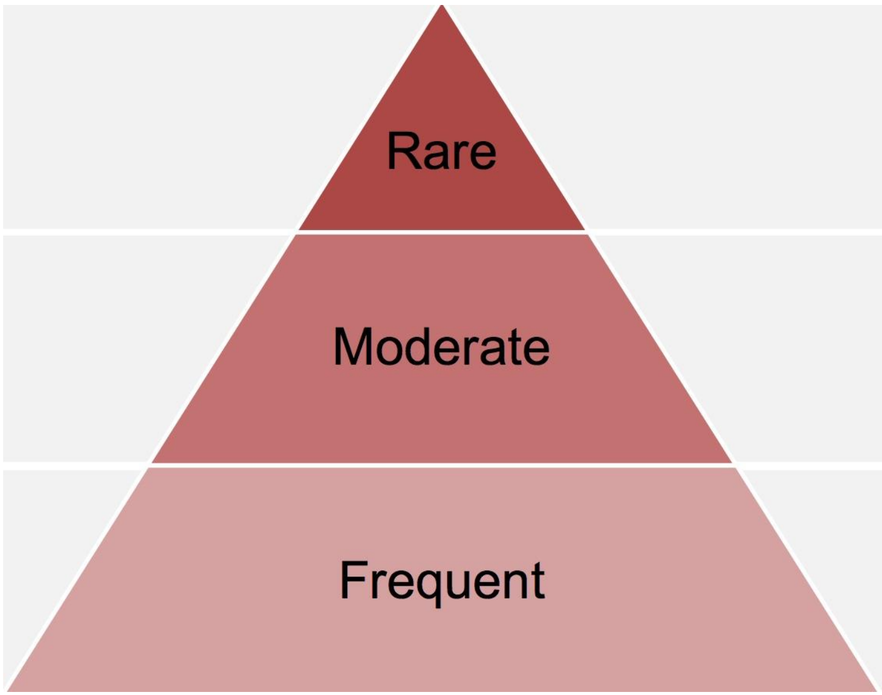


Table 3 **Main echocardiographic findings in takotsubo syndrome**

LV systolic function	Marked reduction in LVEF on admission with improvement at short term
LV WMAs	• Independent of the distribution of epicardial coronary artery (circumferential pattern) • Apical ballooning • Variant form: mid-ventricular ballooning; inverted TTS
RV involvement	Reverse McConnell sign (biventricular ballooning)
Speckle-tracking	Circumferential impairment of LV longitudinal and radial strain
Coronary flow	• Preserved distally to the coronary artery • Coronary flow reserve is impaired in the acute phase

EF, ejection fraction; LV, left ventricular; RV, right ventricular; TTS, takotsubo syndrome; WMAs, wall motion abnormalities.

Prevalence of complications in TTS in INTER-TAK registry



Tachyarrhythmia (2-5%)
Bradyarrythmia (2-5%)
Torsades des Pointes (2-5%)
Death (1-4.5%)
Ventricular tachycardia/fibrillation ~3%
Acute ventricular septal defect <1%

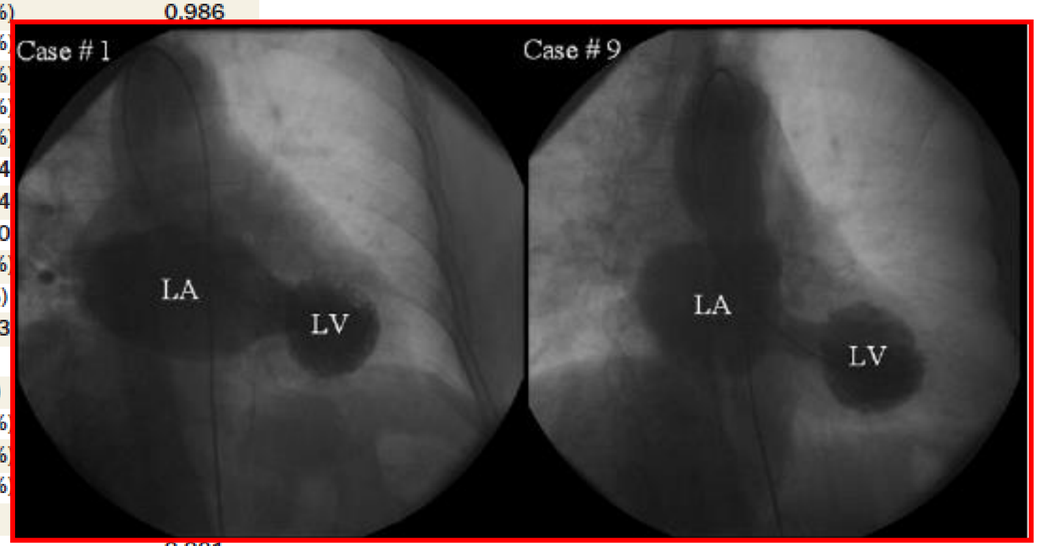
Atrial Fibrillation (5-15%)
LV-Thrombus (2-8%)
Cardiac Arrest (4-6%)
AV-Block ~5%

Acute Heart Failure (12-45%)
LVOTO (20-25%)
Mitral Regurgitation (14-25%)
Cardiogenic Shock (6-20%)

Left Ventricular Apical Ballooning Syndrome as a Novel Cause of Acute Mitral Regurgitation

Table 1 Baseline Clinical and Echographic Characteristics of Patients With and Without Significant Acute Mitral Regurgitation

Variable	Overall Study Group (n = 68)	Patients With Acute Mitral Regurgitation (n = 14)	Patients Without Acute Mitral Regurgitation (n = 54)	p Value
Age (yrs)	74 ± 10	76 ± 7	74 ± 10	0.349
Female	64 (94%)	14 (100%)	50 (93%)	0.294
Hypertension	39 (57%)	8 (57%)	31 (57%)	0.986
Diabetes mellitus	7 (10%)	1 (7%)	6 (11%)	
Hypercholesterolemia	26 (38%)	4 (29%)	22 (41%)	
Smoker	14 (21%)	3 (21%)	11 (20%)	
Antecedent stressful event*	49 (72%)	9 (64%)	40 (74%)	
Systolic blood pressure (mm Hg)	122 ± 24	113 ± 22	124 ± 24	
Diastolic blood pressure (mm Hg)	71 ± 14	67 ± 16	71 ± 14	
Heart rate (beats/min)	89 ± 19	93 ± 18	88 ± 20	
ST-segment elevation	51 (75%)	11 (79%)	40 (74%)	
Killip class III or IV	14 (21%)	7 (50%)	7 (13%)	
Creatine kinase-MB peak (U/l)	28 ± 43	57 ± 83	21 ± 33	
Time to peak creatine kinase (h)	5 ± 6	5 ± 5	5 ± 6	
Intra-aortic balloon pump use	9 (13%)	5 (36%)	4 (7%)	
Calcium channel blockers at discharge	10 (15%)	0	10 (19%)	
Beta-blockers at discharge	37 (54%)	9 (64%)	28 (52%)	
ACE inhibitors or angiotensin receptor blockers at discharge	53 (78%)	10 (71%)	43 (80%)	
LV internal diameter (mm)	46 ± 5	47 ± 5	46 ± 5	
EF on admission (%)	33 ± 9	26 ± 7	35 ± 9	0.001
EF at discharge (%)	49 ± 10	41 ± 11	52 ± 9	0.001
LVEF >50% at discharge	36 (53%)	3 (21%)	33 (61%)	0.008
Time to EF ≥50% (days)	7 ± 4	9 ± 4	7 ± 4	0.057
Mitral SAM	7 (10%)	5 (36%)	2 (4%)	<0.0001
With mitral-septal contact	4 (6%)	3 (21%)	1 (2%)	0.045
Mitral regurgitation grade	1.4 ± 1.1	3.1 ± 0.5	0.9 ± 0.7	<0.0001



Parodi G, et al. JACC 2007

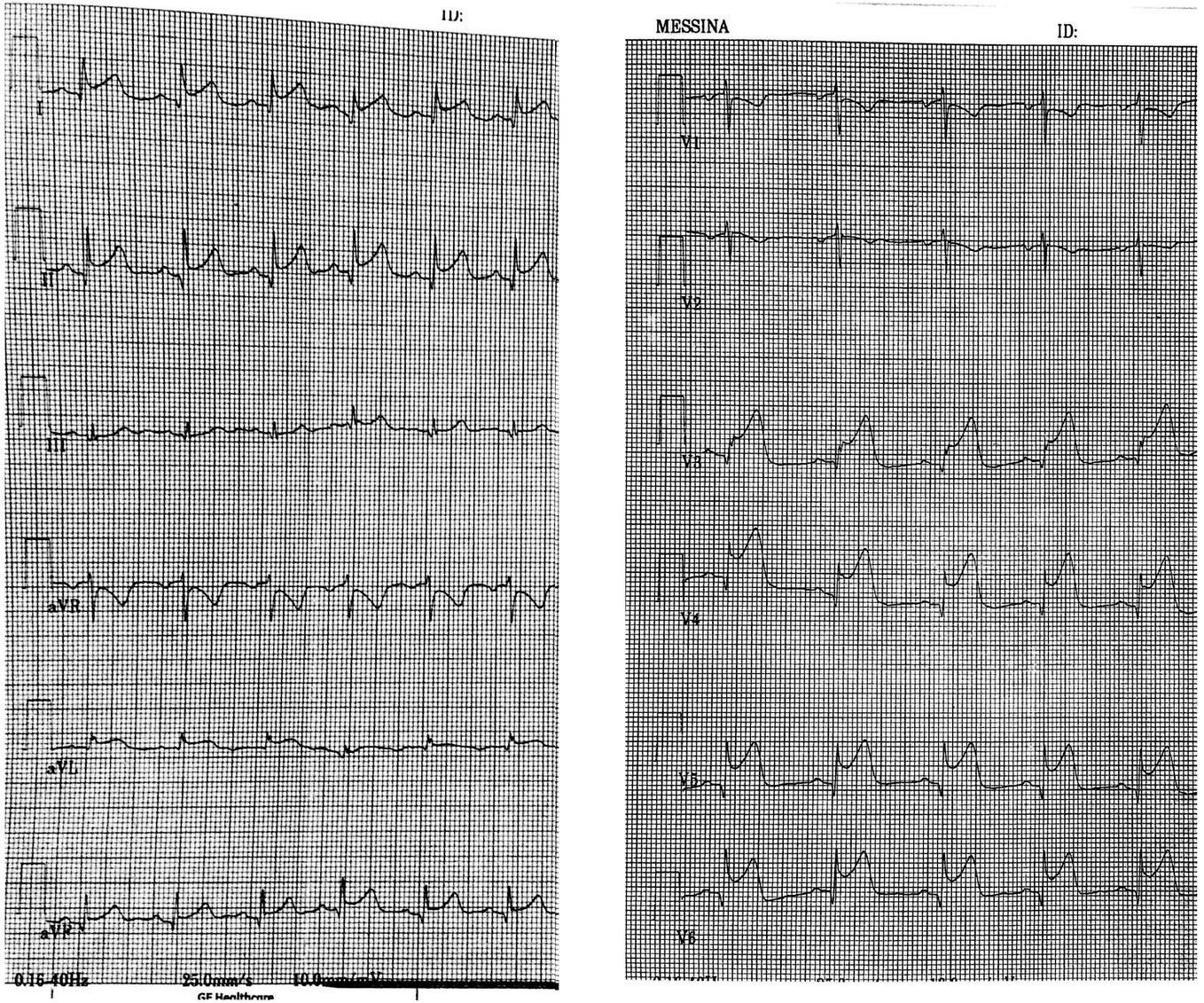
58 years old post-menopausal woman

No risk factors for CAD
Mood disorder

Admitted in the ER of our Hospital for retrosternal chest pain

(Of note she reported the onset of chest pain immediately after the scare for risking a road crash with her car)

ECG



ECG anterior ST elevation

FAST ECHO: akinesia of the LV apical segments

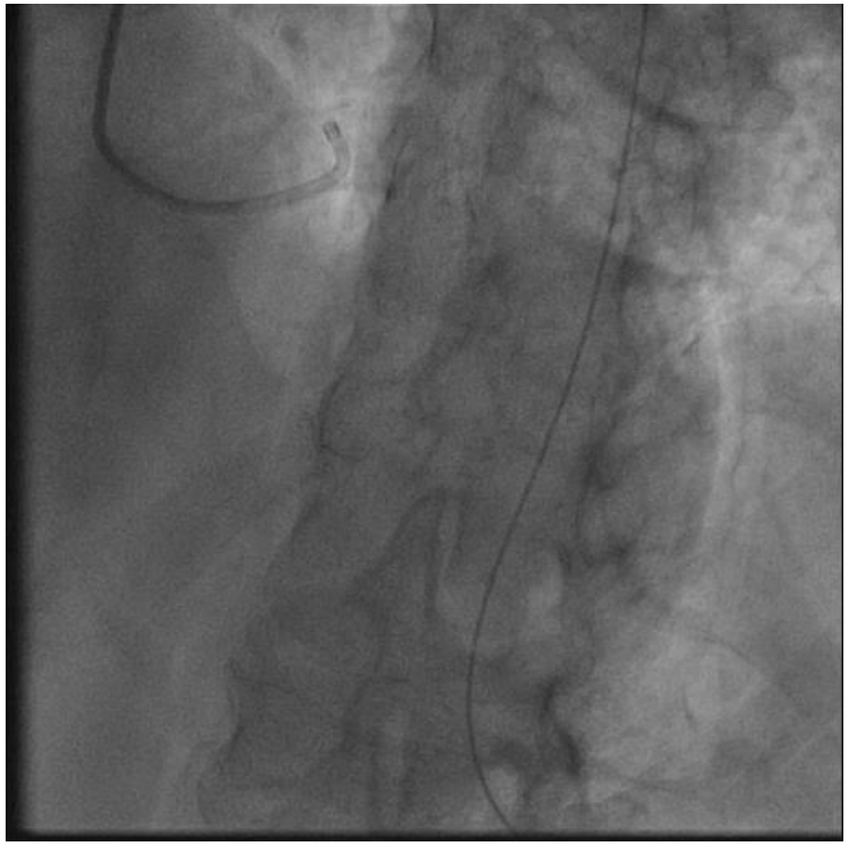
TnI: 0,4 ng/ml

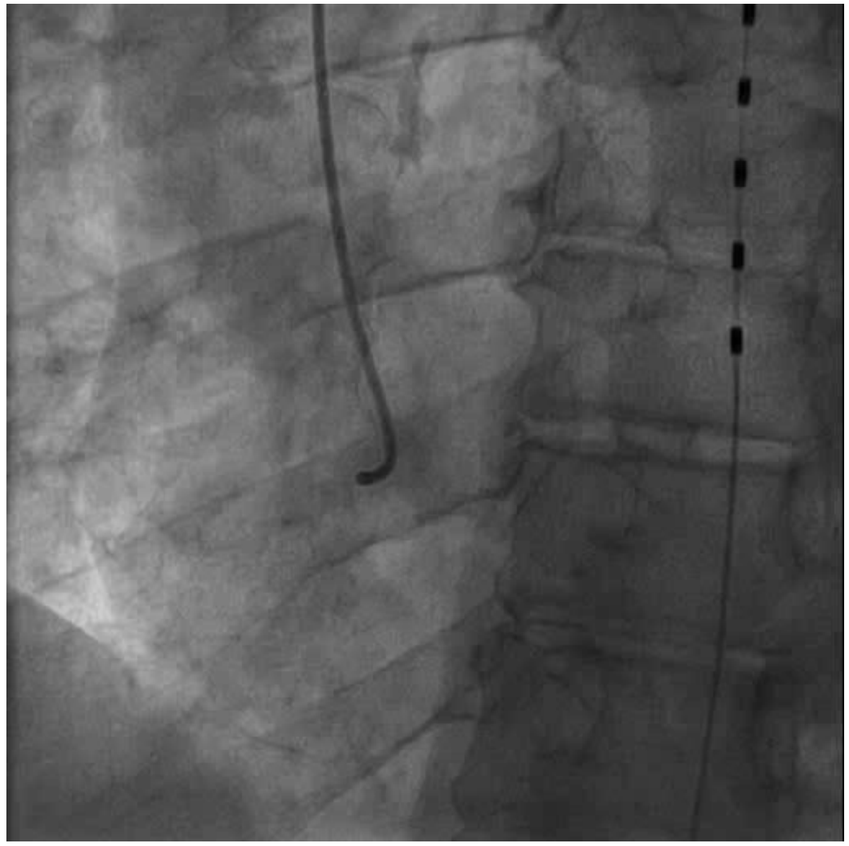
Code: anterior STEMI

Medical treatment
•Enoxaparina,
•ASA,
•ticagrelor and
•atorvastatin

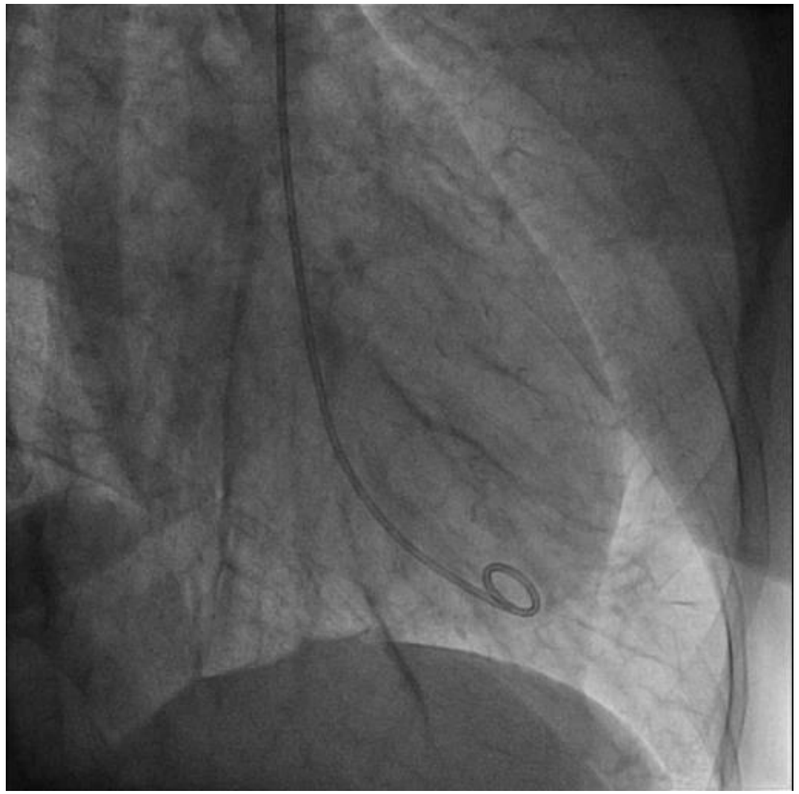
•,,,,,,,,,in cath-lab to perform urgent coronary angıography

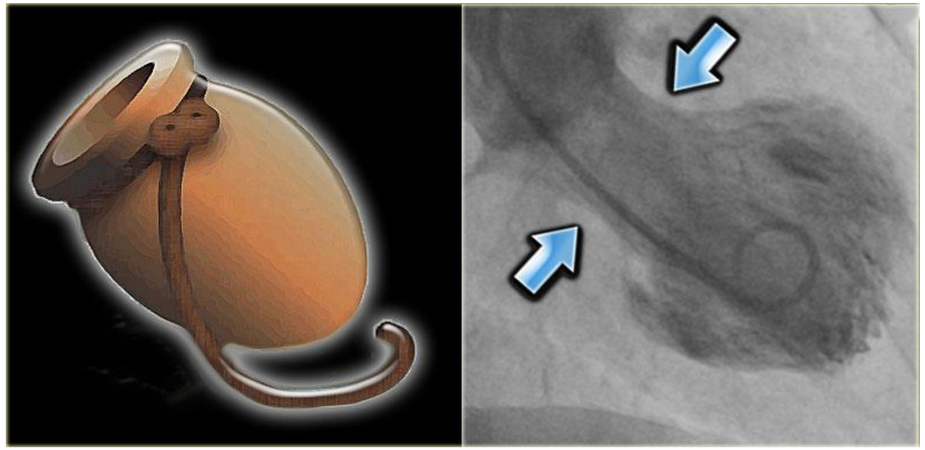
Coronary Angiography





VENTRICULOGRAPHY





Takotsubo syndrome

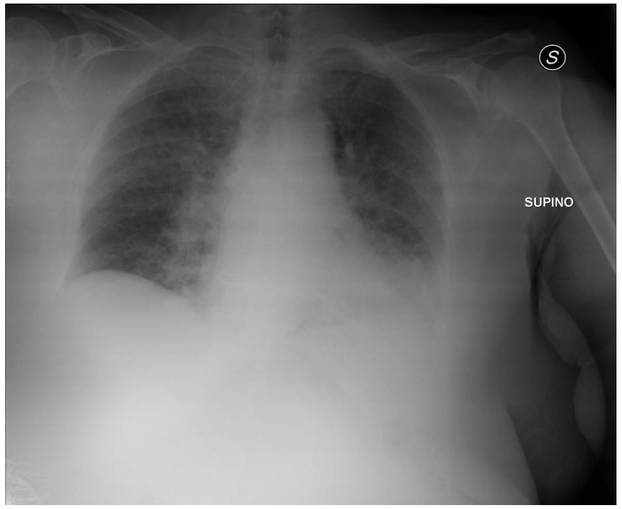
CCU admission

Patient developed dyspnea and profuse sweating

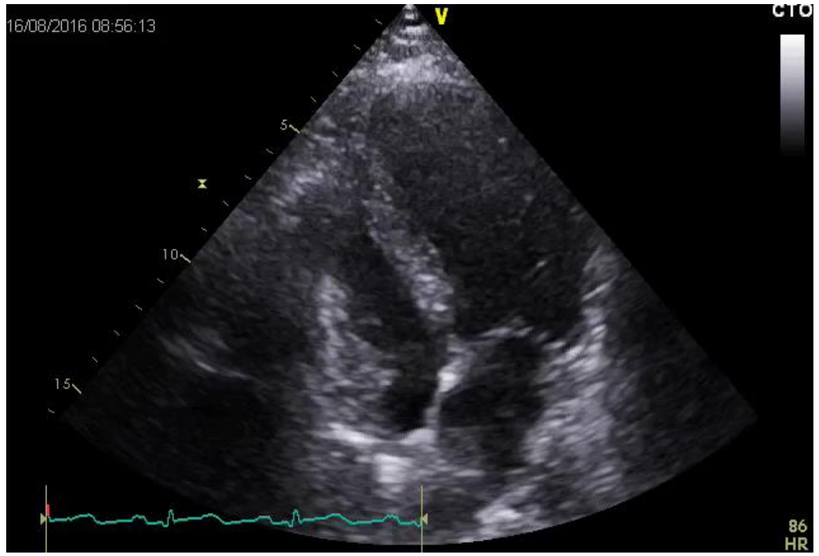
Heart: pansystolic murmur at the apex
Chest: mid-basal pulmonary rales

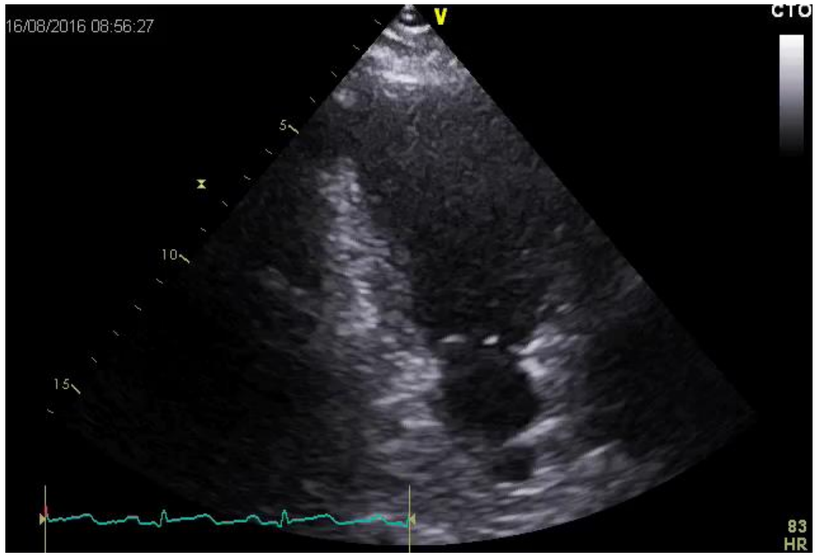
BNP: 867 pg/ml

AP = 88/56 mmHg
HR = 91/min
SpO_2 = 81%;
pO_2 = 66 mmHg
pCO_2 = 17 mmHg
pH 7,54

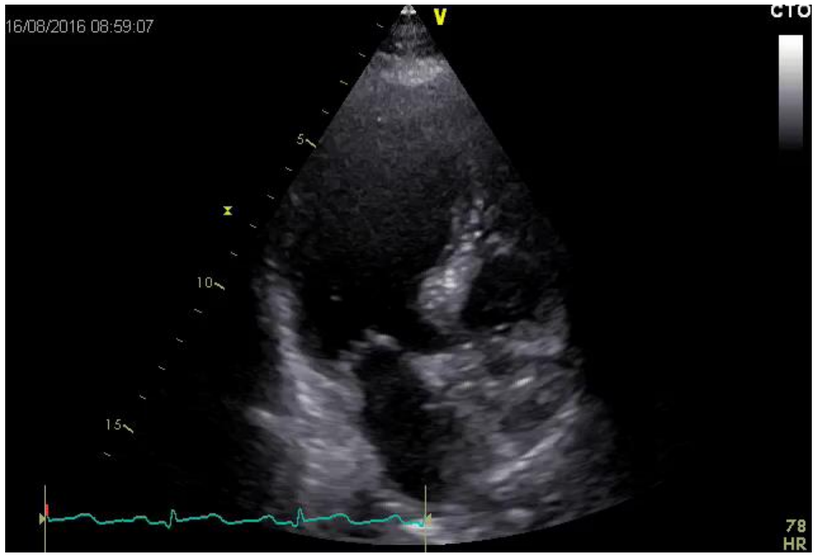


TTE

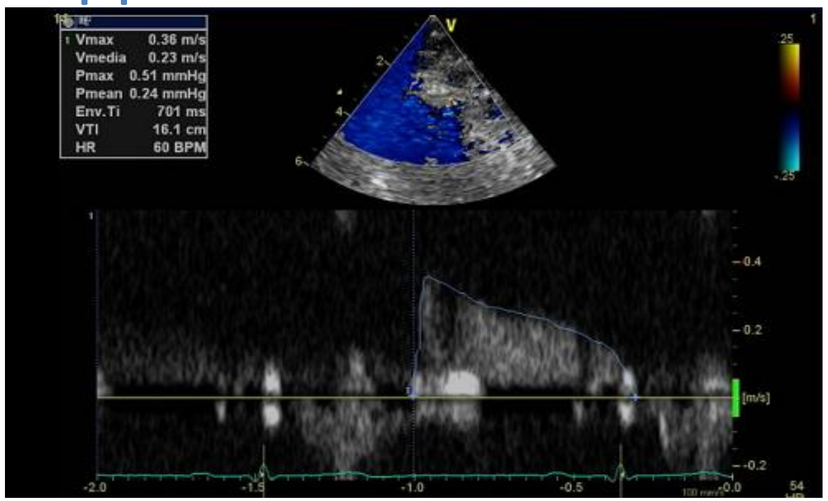




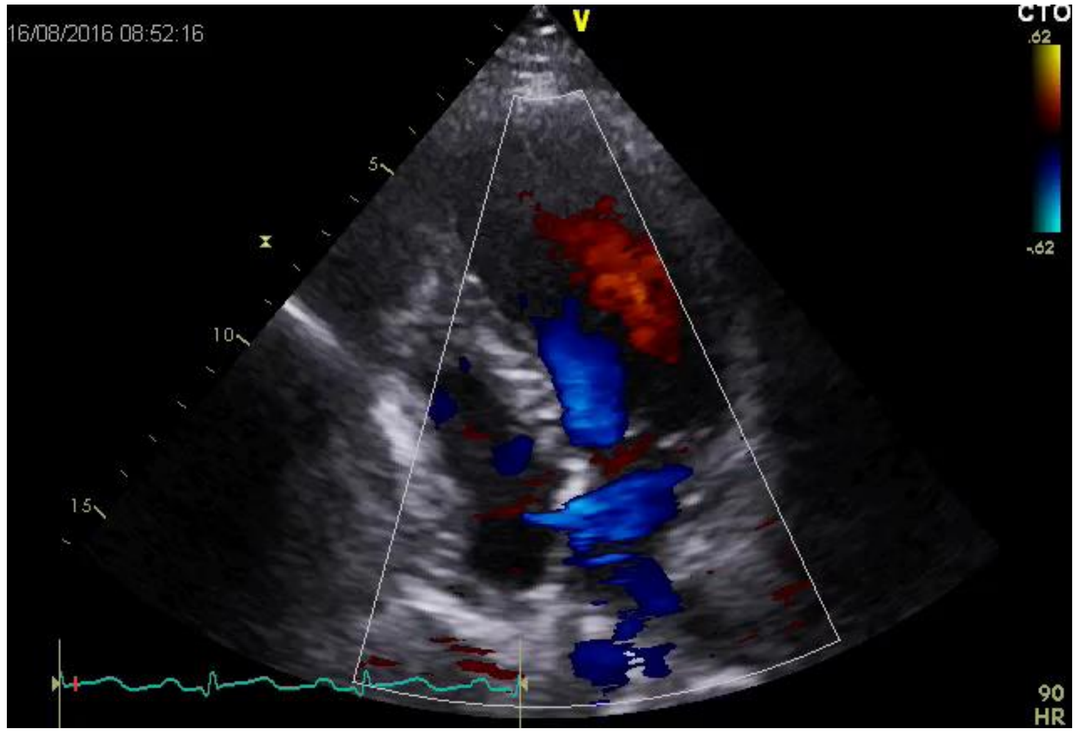
- **EF = 40%**
- **Akinesia of the LV apex**
- **Hyperkinesia oh the LV basal segments**



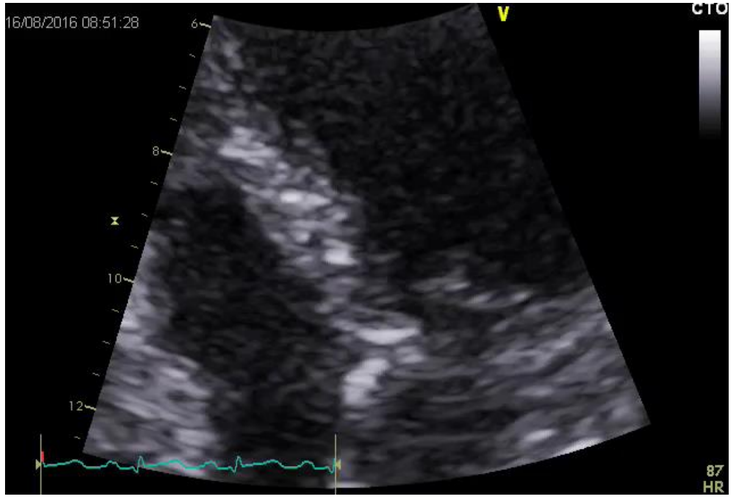
PW Doppler evidence of flow in distal LAD

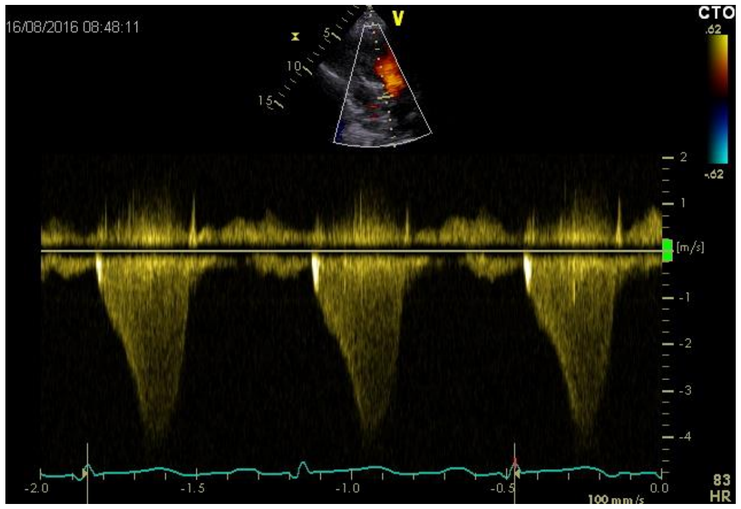


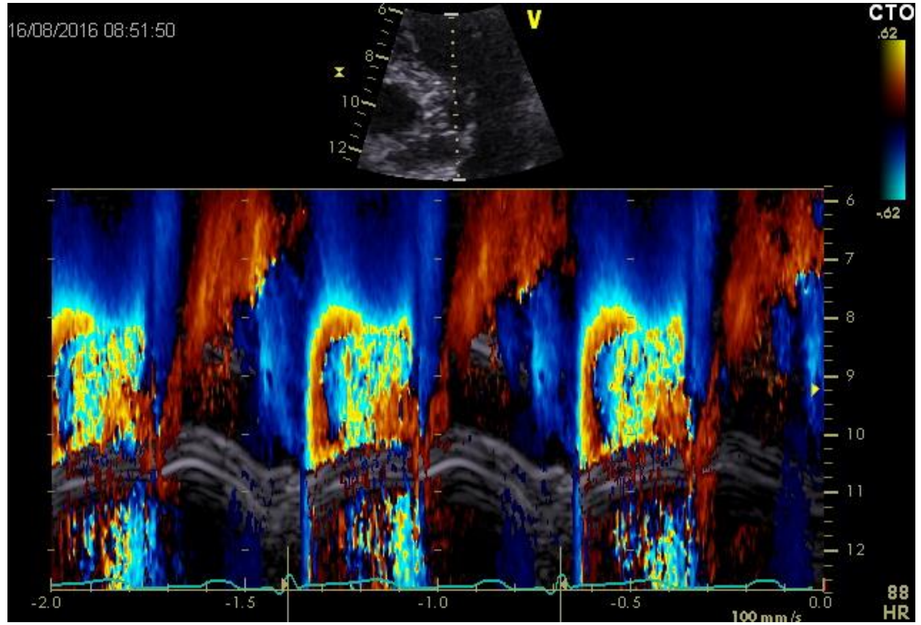
Severe functional MR



LVOTO







Color M-mode of LVOT showing systolic aliasing

Vmax = 3.89 m/sec
Intraventricular gradient = 60.52 mmHg

Cardiogenic shock patient with takotsubo syndrome complicated by LVOTO and mitral regurgitation

How do you treat?

a) Levosimendan + loop diuretic

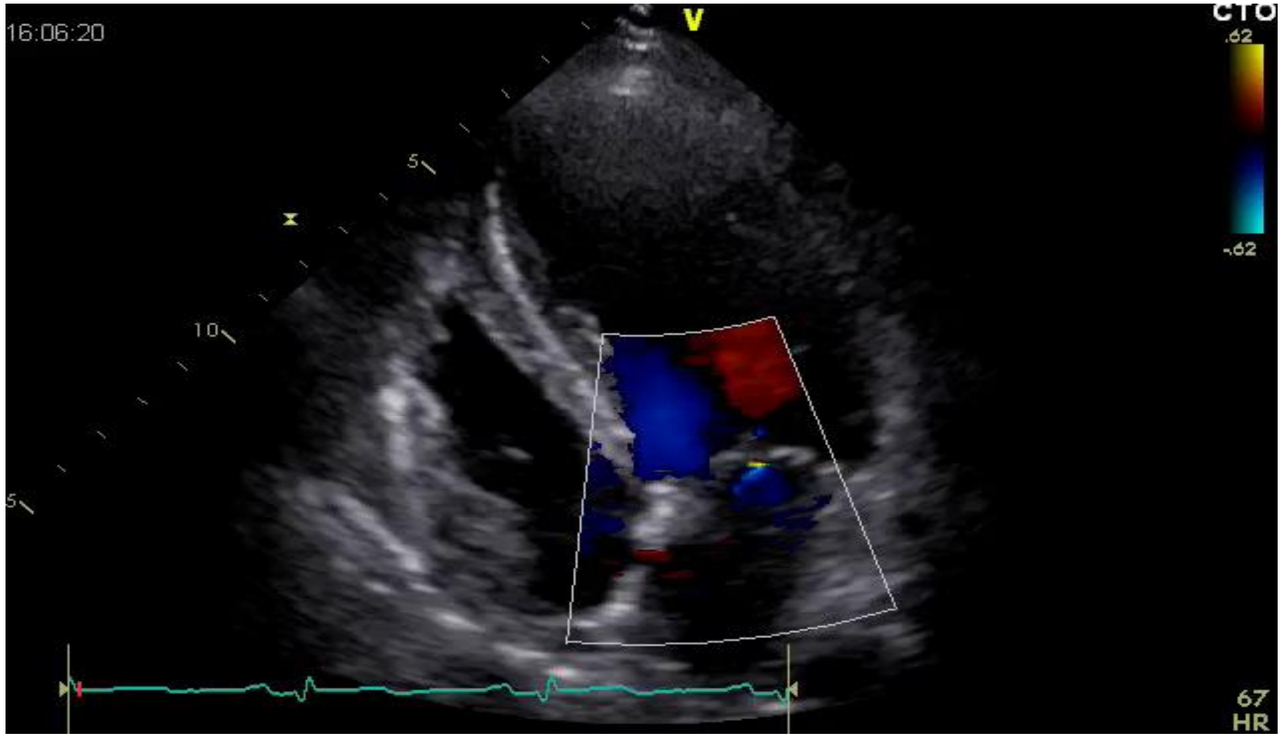
b) Inotropic agents + loop diuretic

c) Intraortic balloon pump + loop diuretic

d) Metoprolol + loop diuretic

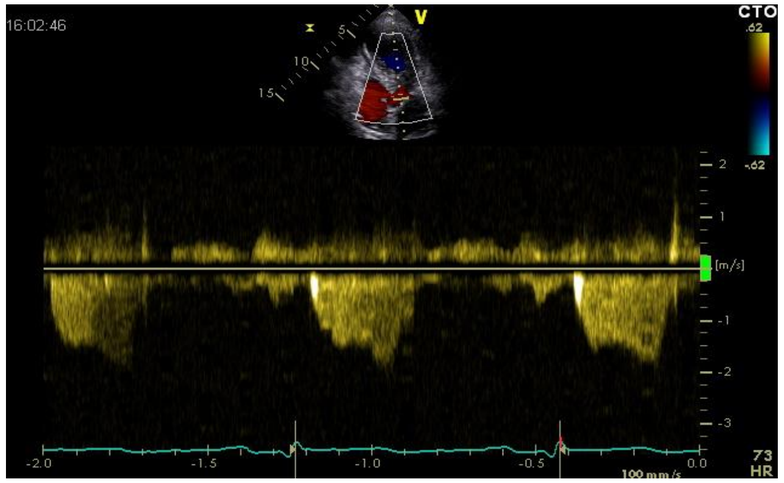
e) Esmolol followed by metoprolol + loop diuretic

The day after…TTE

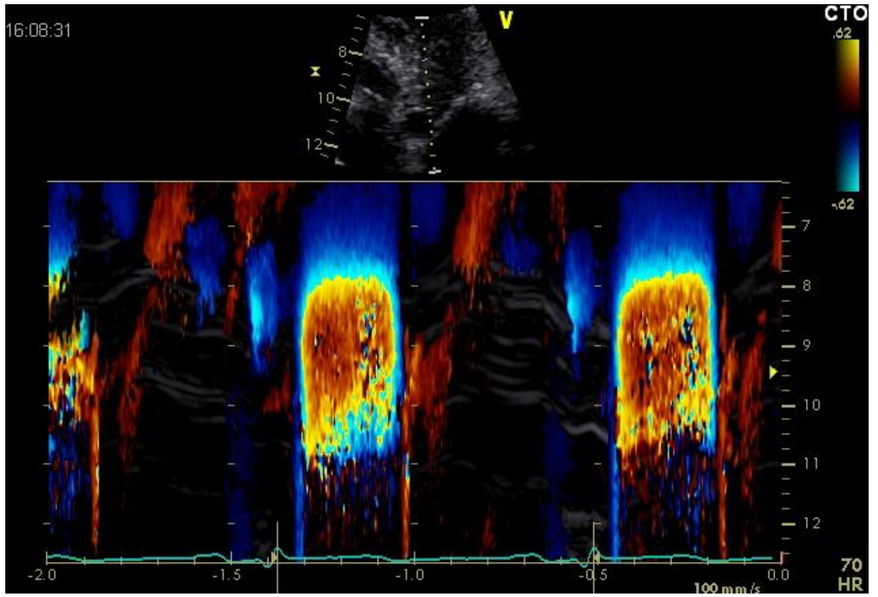


Mild MR

The day after…TTE



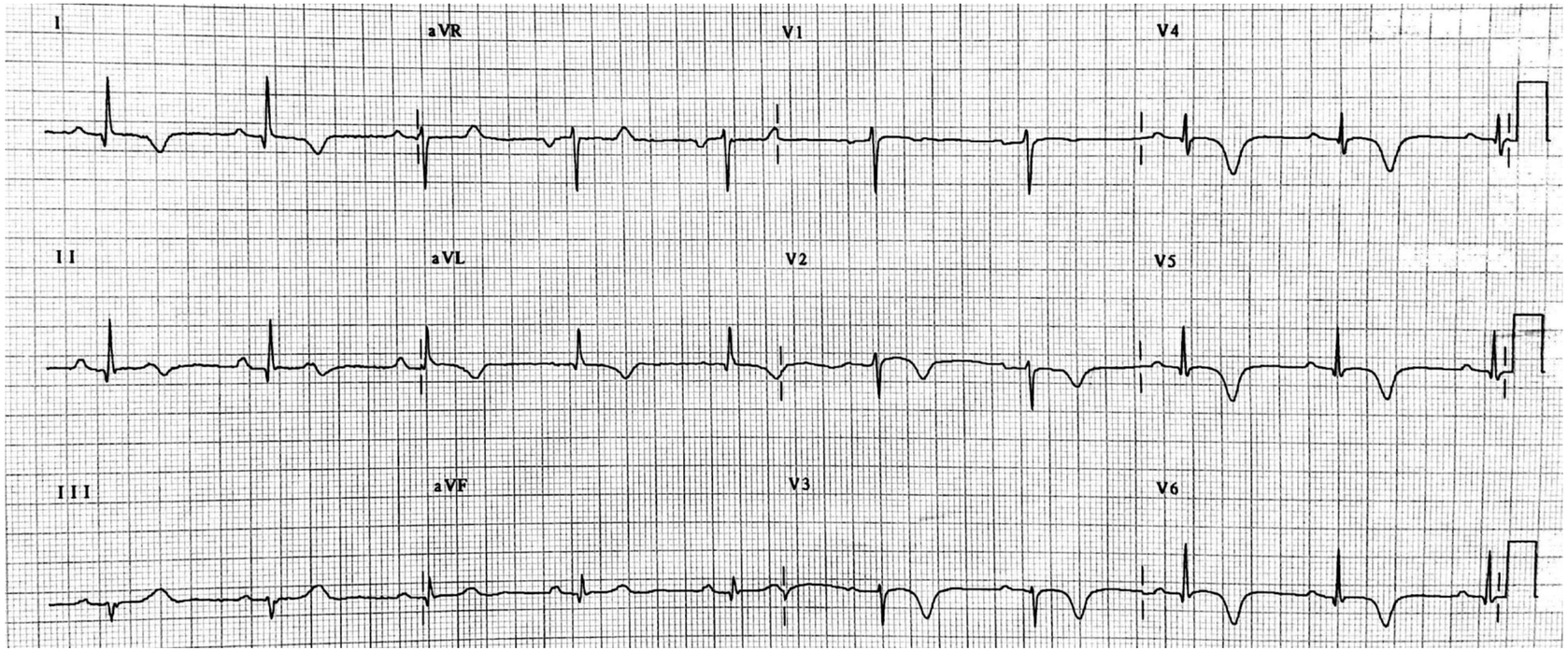
Vmax = 1.99 m/sec
Grad Max = 15.79 mmHg



No evidence of aliasing at
Color M-mode of LVOT

At 1 month follow up…

ECG

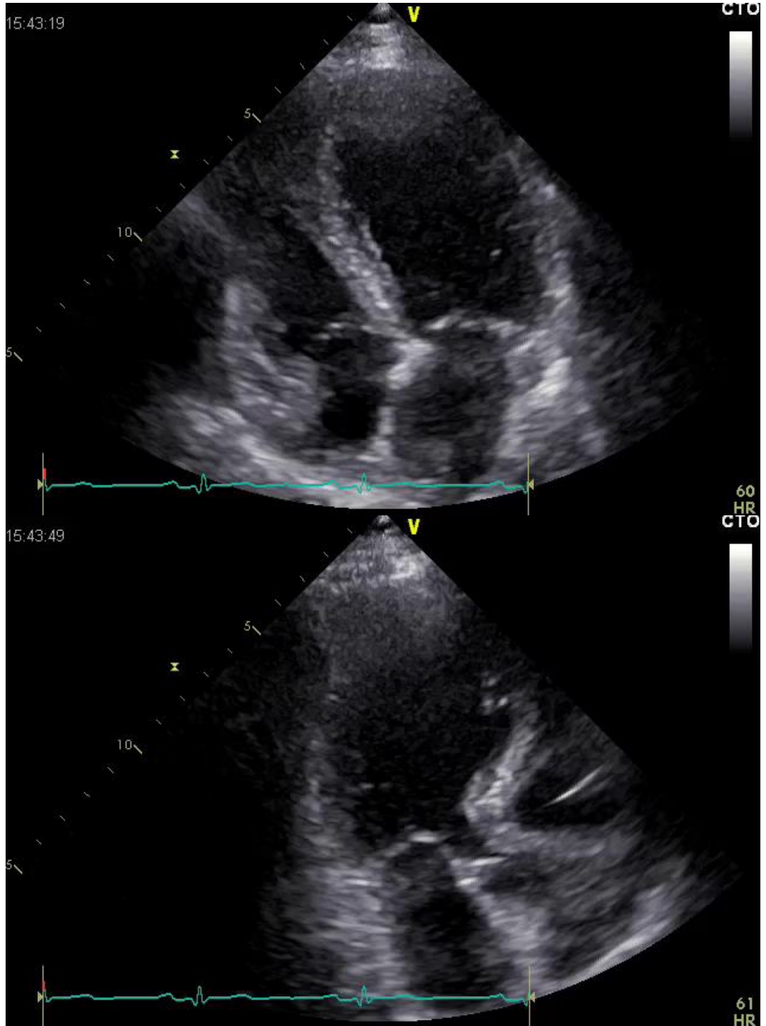


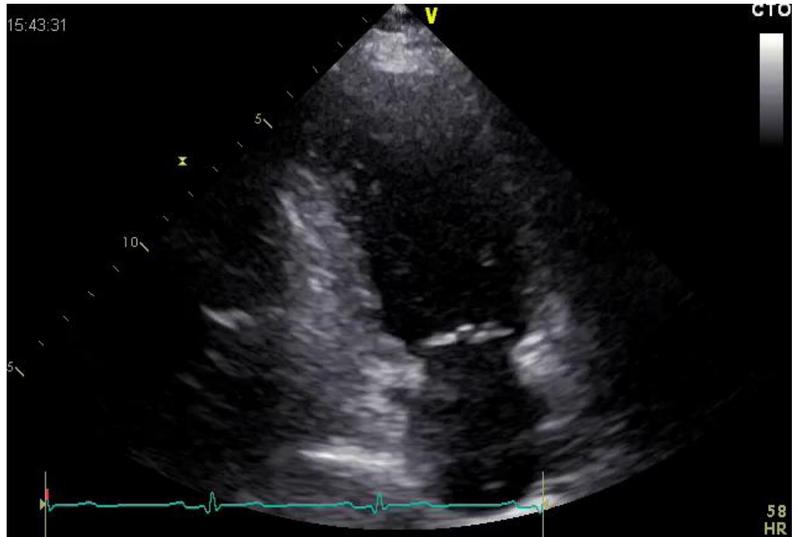
At 1 month follow up…

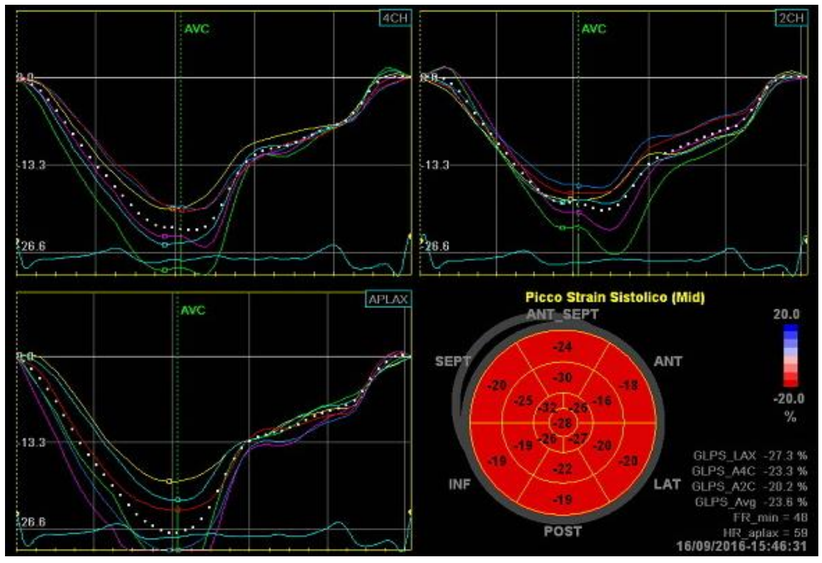
TTE

- EF = 62%
- No evidence of WMA

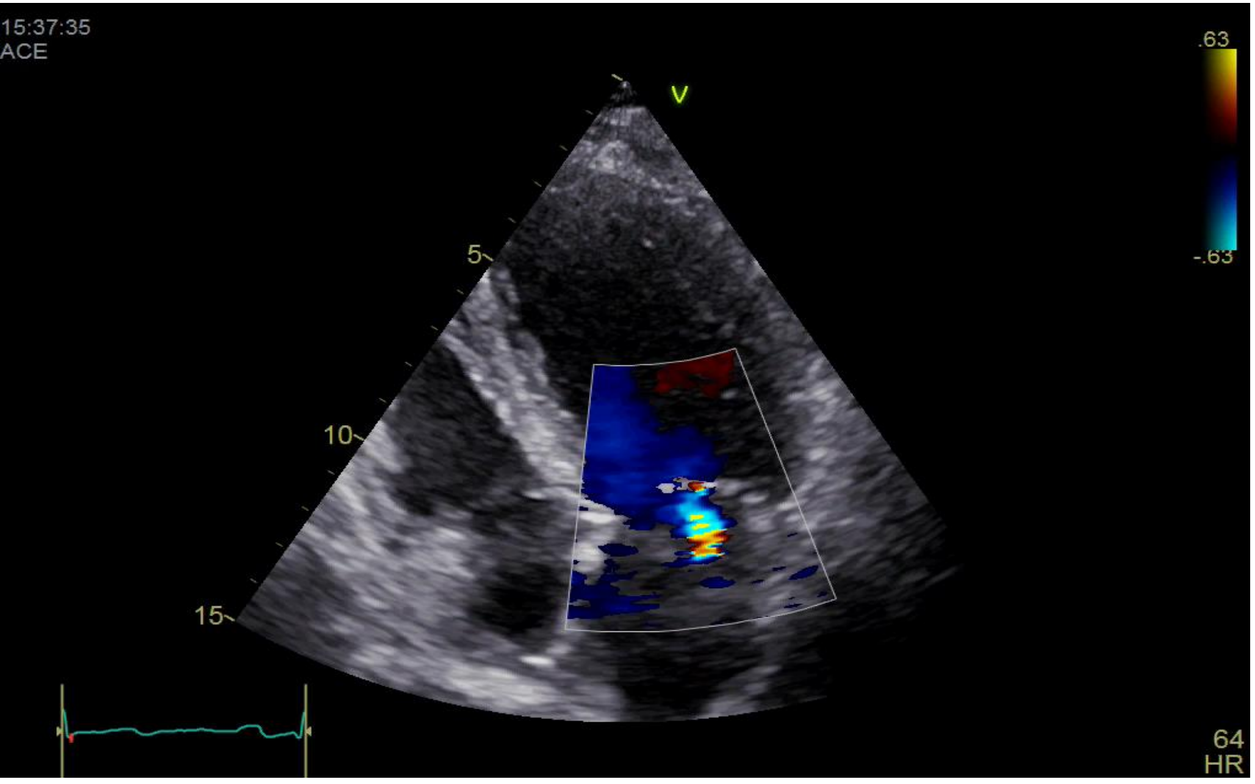
GLS = -23.6%



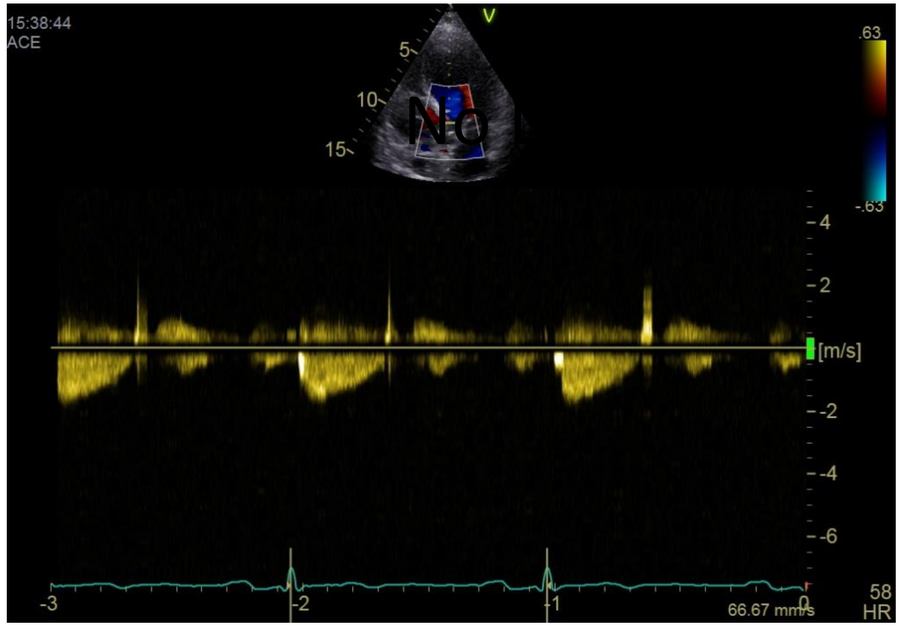




At 1 month follow up…
TTE



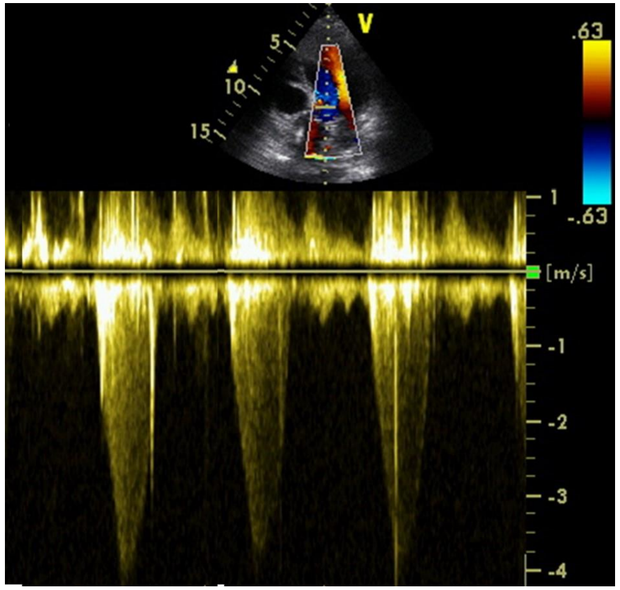
Mild MR



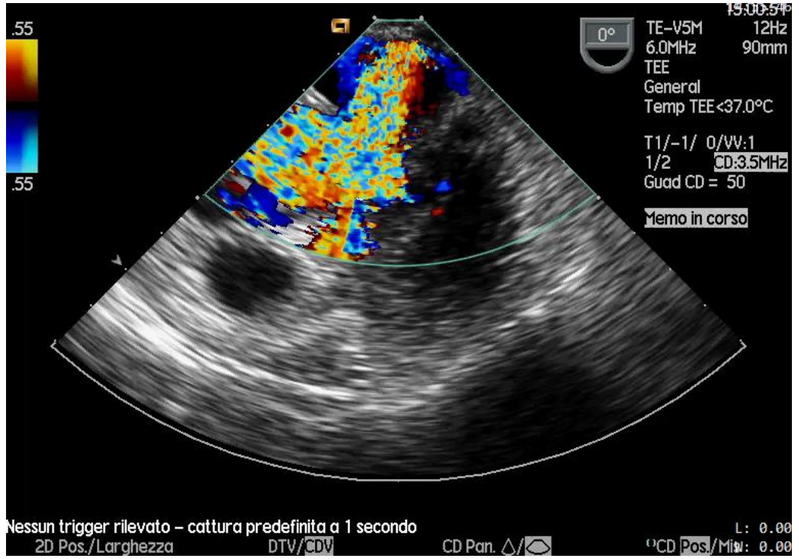
Clinical case

During catheterization, the patient was restless, cold, clammy, and with severe systemic hypotension (70/40 mmHg).

Owing to the blood desaturation to 82%, oxygen therapy delivered by facemask was promptly started.



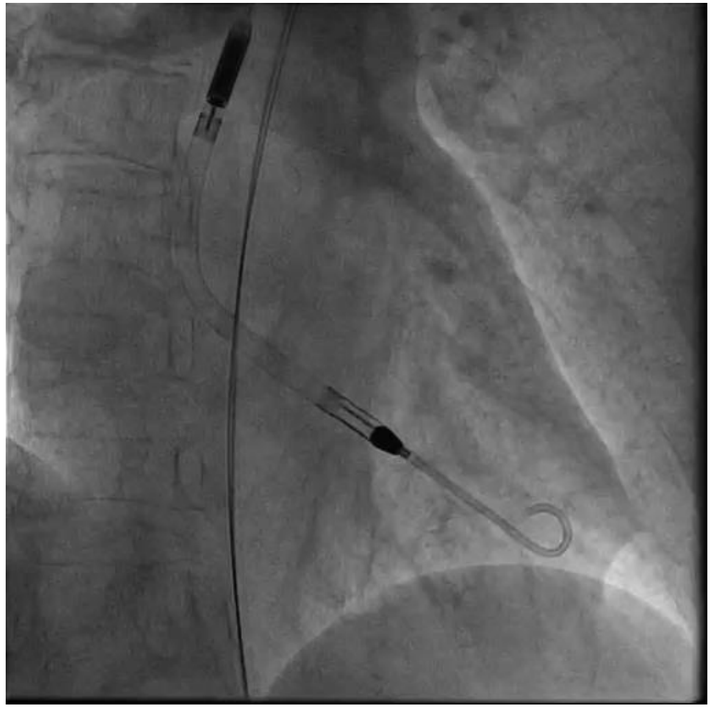
Intraventricular pressure gradient (Peak gradient of 71 mmHg)

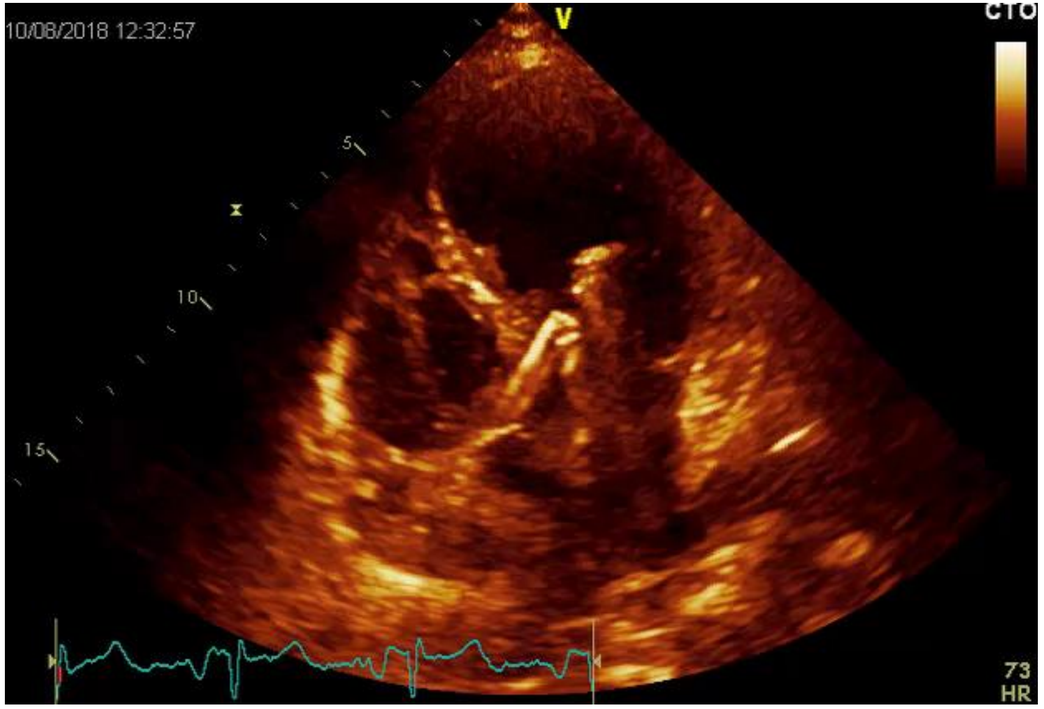


Severe MR

Clinical case

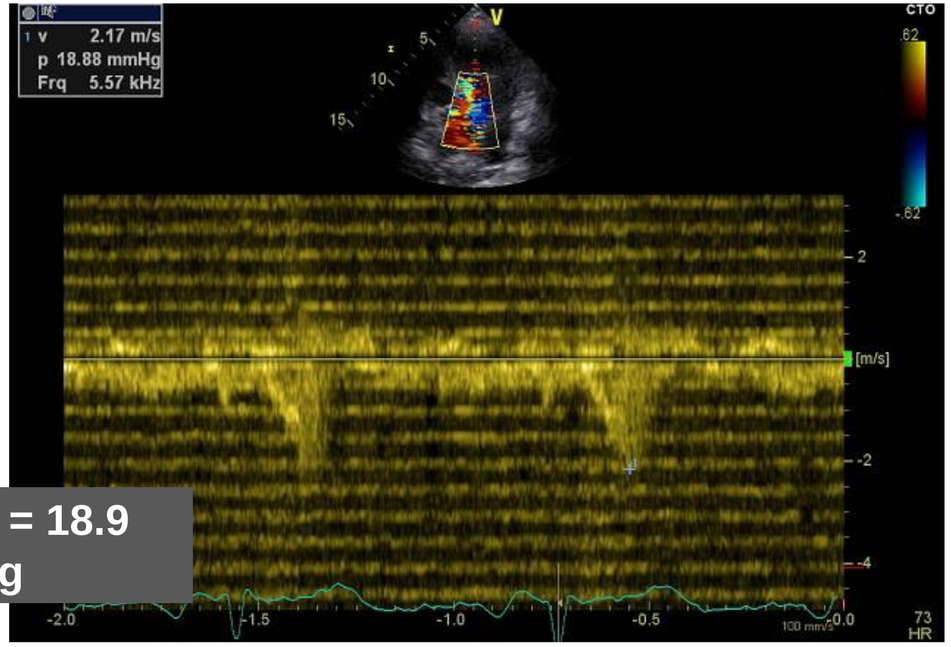
Owing to the persistence of a poor hemodynamic condition, an **Impella CP®** assist device (Abiomed, Danvers, Massachusetts) was placed throught the right femoral artery

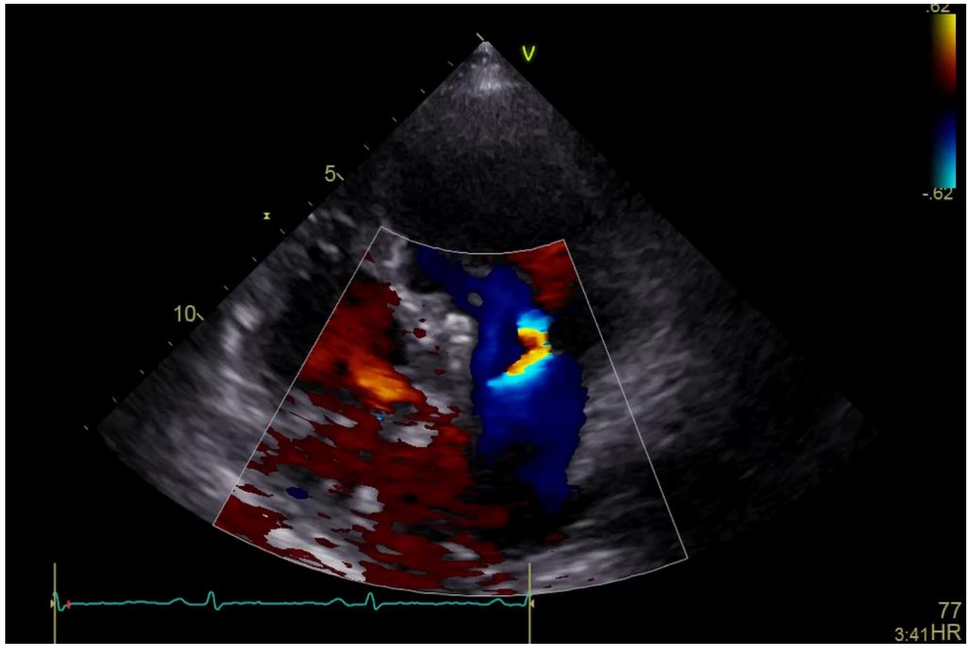




Clinical case

The hemodynamic status promptly improved (blood pressure increased to 95/60 mmHg) and oxygen saturation raised to 93%.





Peak Grad = 18.9 mmHg

Clinical case

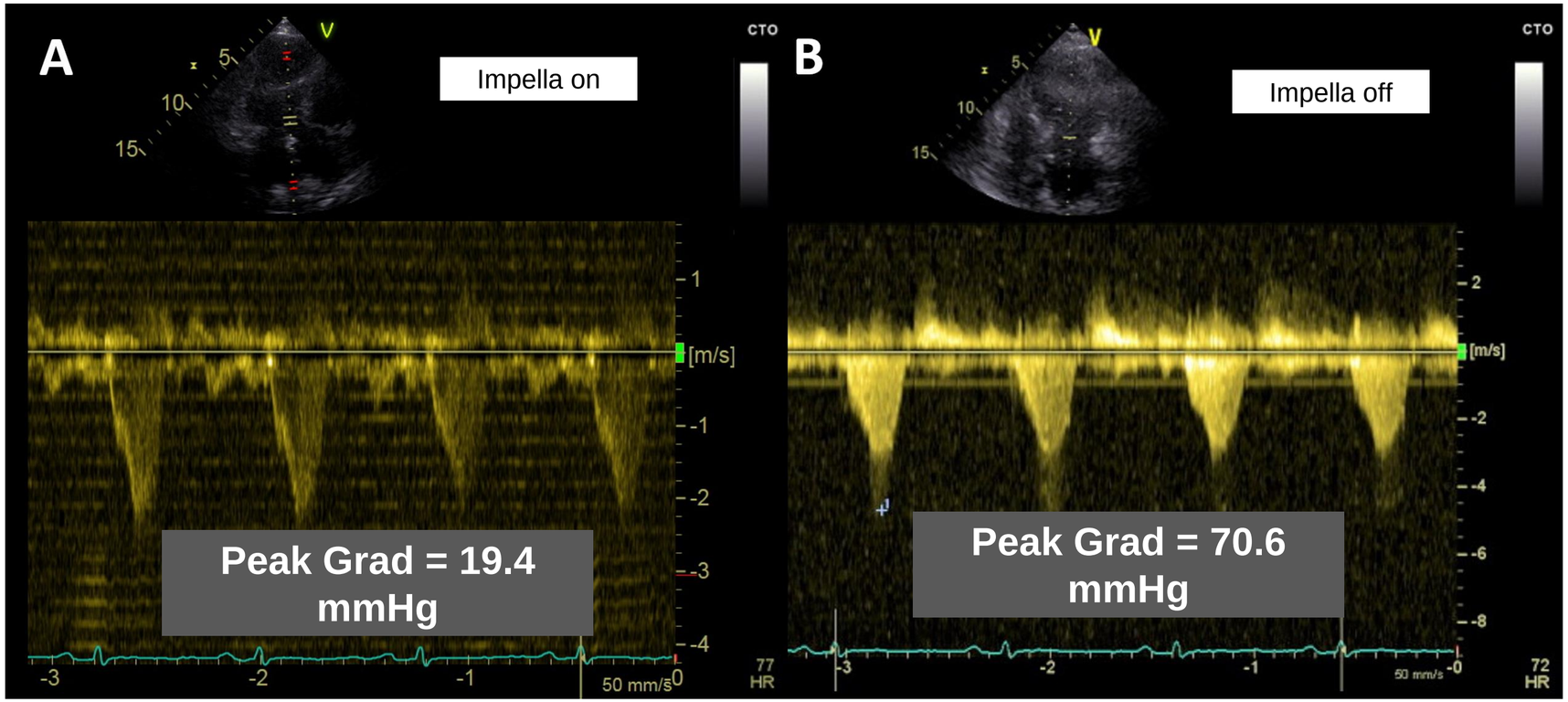
The patient was transferred to the cardiac care unit (CCU) where she was maintained on adequate hydration, low dose (0.1 µg/kg/min) noradrenalin infusion and Impella support.

the next two days, the patient’s clinical status further improved and she was successfully titrated off vasopressorsOver

LV EF: 40%

Clinical case

However, LVOTO persisted at the attempt to wean off the patient from the Impella assistance

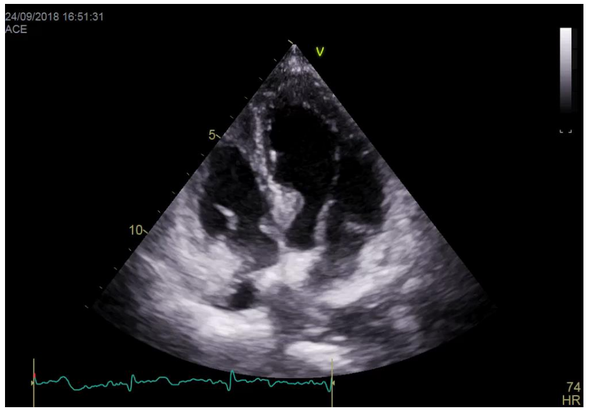


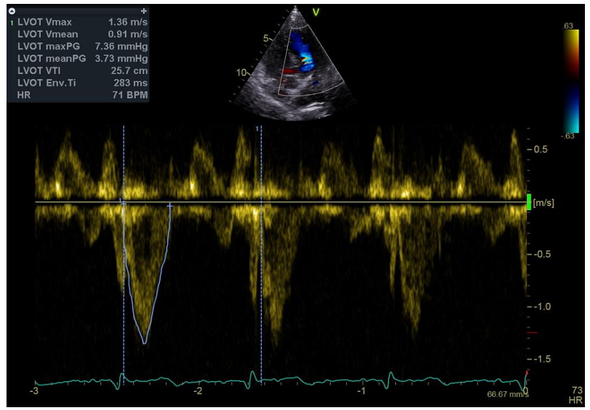
Clinical case

At day 5, TTE showed a further improvement of LV EF (50%) and the disappearance of the dynamic LVOTO during prolonged standby of the mechanical circulatory support (MCS). Impella was removed.

The patient was discharged after one week in stable hemodynamic and clinical conditions with beta-blockers and ACE inhibitor. BNP was 360 pg/ml.

At one month, TTE confirmed the complete recovery of WMA and LV systolic function (LV EF: 60%), mild MR and absence of LVOTO.





Impella in unstable TTS patient with LVOTO

Early MCS with Impella may provide a reasonable therapeutic approach in patients with cardiogenic shock due to TTS complicated by LVOTO and severe MR.

The Impella device, by propelling blood from the LV into the ascending aorta, allows skipping the LVOTO and the maintenance of the systemic pressure.

This benefit may be observed after implantation as well as during CCU course, before LV function recovery and LVOTO disappearance (bridge-to-recovery).

ORIGINAL RESEARCH

Echocardiographic Correlates of Acute Heart Failure, Cardiogenic Shock, and In-Hospital Mortality in Tako-Tsubo Cardiomyopathy

Rodolfo Citro, MD,*† Fausto Rigo, MD,‡ Antonello D'Andrea, MD,§ Quirino Ciampi, MD,‖ Guido Parodi, MD,¶ Gennaro Provenza, MD,# Raffaele Piccolo, MD,** Marco Mirra, MD,†† Concetta Zito, MD,‡‡ Roberta Giudice, MD,†† Marco Mariano Patella, MD,§§ Francesco Antonini-Canterin, MD,‖‖ Eduardo Bossone, MD,† Federico Piscione, MD,†† Jorge Salemo-Uriarte, MD,* on behalf of the Tako-Tsubo Italian Network Investigators

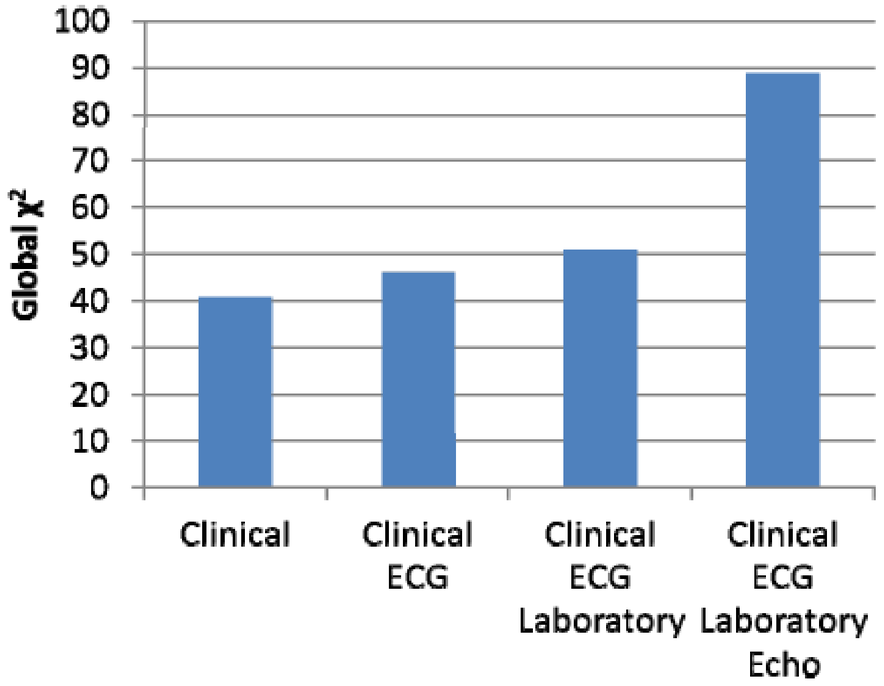
227 pts
Major adverse events in 59 pts

Table 5. Hazard ratio (95% CI) for the major adverse events (acute heart failure, cardiogenic shock, and in-hospital mortality) in univariate and multivariate models.

Variables	Wald Chi-square	P-value	HR	95% CI	Wald Chi-square	P-value	HR	95% CI
Age ≥ 75	7.162	0.007	2.353	1.257-4.403	4.270	0.039	2.818	1.055-7.529
Heart rate	4.492	0.034	1.020	1.001-1.038				
Chest pain with dyspnea	9.552	0.002	3.477	1.578-7.664				
BNP	3.385	0.049	1.002	1.000-1.004				
LVEF	15.398	< 0.001	0.892	0.842-0.944	18.400	<0.001	0.923	0.890-0.958
E/e' ratio	23.345	< 0.001	1.266	1.150-1.393	6.410	0.011	1.131	1.028-1.244
sPAP	23.549	< 0.001	1.086	1.050-1.122				
Moderate to severe MR	23.532	< 0.001	5.916	2.885-12.133	5.049	0.025	3.254	1.163-9.109
RV involvement	11.957	0.001	3.845	1.792-8.250				
LVOT obstruction	7.992	0.005	3.173	1.425-7.067				

BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MR: mitral regurgitation; RV: right ventricular; sPAP: pulmonary artery systolic pressure.

Citro R, et al. J Am Coll Cardiol Img 2014;7:119–29



CLINICAL AND ECHOCARDIOGRAPHIC CORRELATES OF ACUTE HEART FAILURE, CARDIOGENIC SHOCK AND IN-HOSPITAL MORTALITY IN TAKO-TSUBO CARDIOMYOPATHY

Echocardiography in TTS: additive incremental prognostic value

Citro R, et al. JACC Imaging. Feb 2014

EDITORIAL COMMENT

Role of Echocardiography in Tako-Tsubo Cardiomyopathy

ı(Hons), PhD, Thanh H. Nguyen, MD, MMedSci, PhD

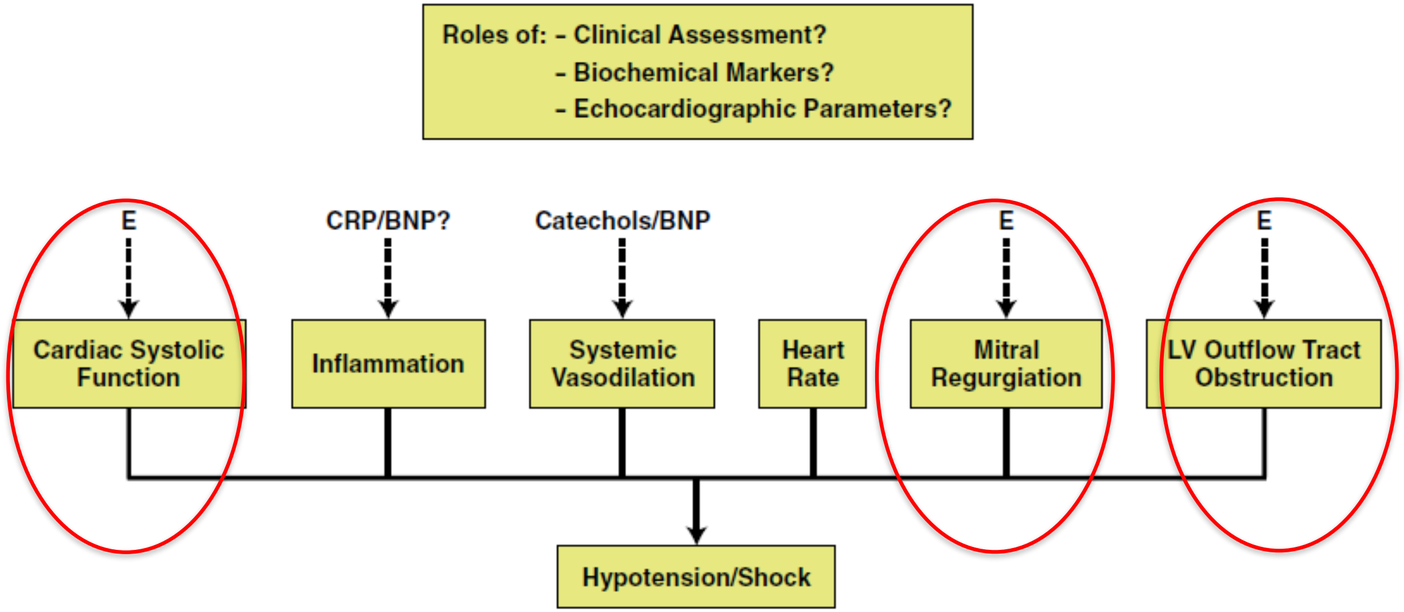
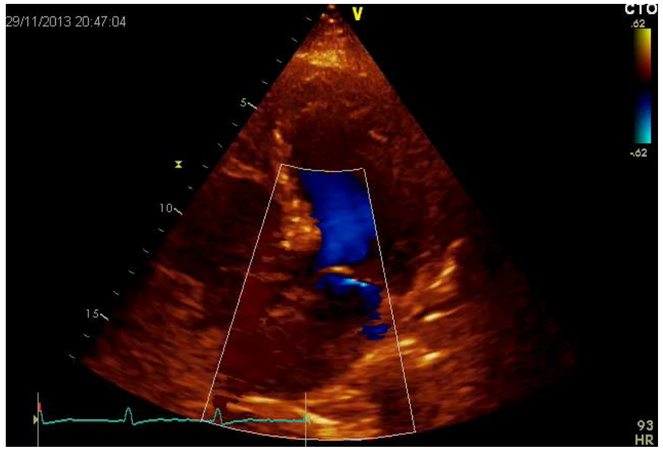
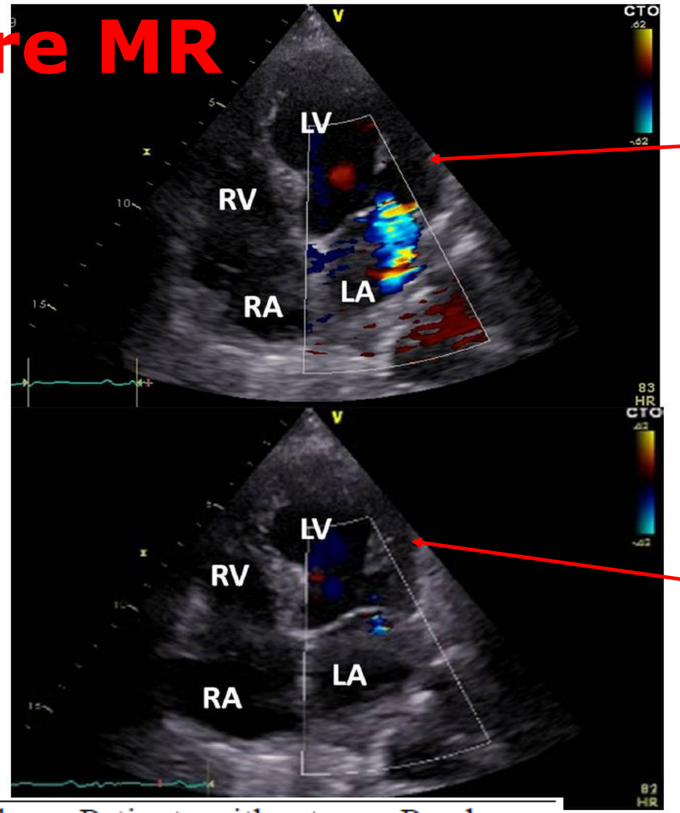


Figure 1. Mechanisms Postulated as Potential Components of Pathogenesis of Hypotension/Shock in TTC

TTS: Reversible moderate to severe MR





Acute phase

Recovery

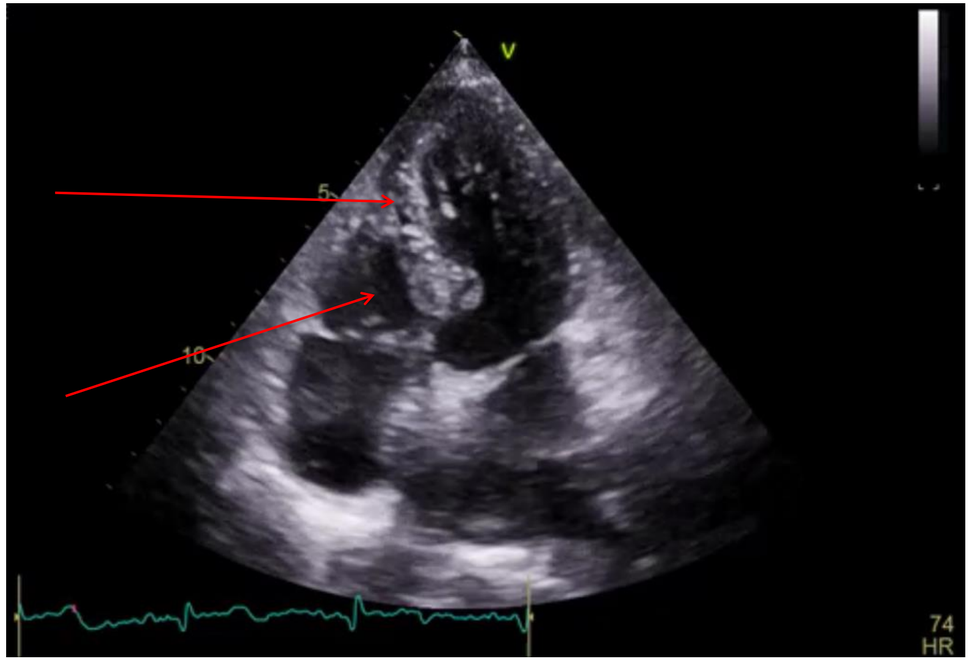
Variables	Overall population (n = 227)	Patients with major complications (n=59)	Patients without major complications (n=168)	P value
Moderate to severe MR	49 (21.5)	29 (49.1)	20 (11.9)	<0.001

Citro R, et al. JACC Imaging. Feb 2014

LVOTO: mechanisms

Small LV cavity

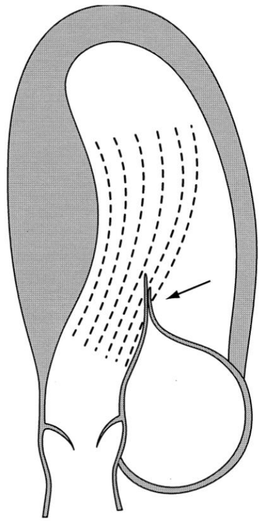
Septal buldge

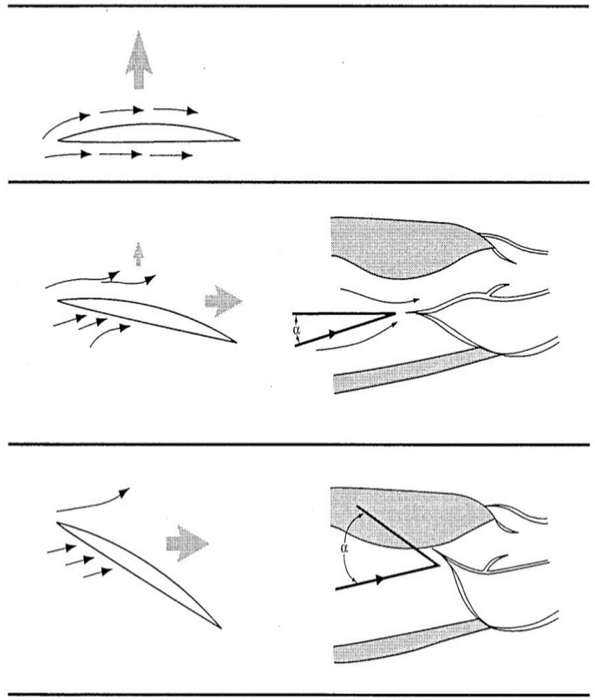


LVOTO may result from basal LV hypercontractility, as occurs in the typical apical ballooning forms of TTS. Small left ventricles and septal bulge are predisposing factors.

Systolic Anterior Motion Begins at Low Outflow Tract Velocity

The pushing force of flow





The protruding leaflets extend into the edge of the flowstream and are swept by the pushing force of flow toward the septum. Flow pushes the underside of the leaflets

Sherrid et al. J Am Coll Cardiol 2000

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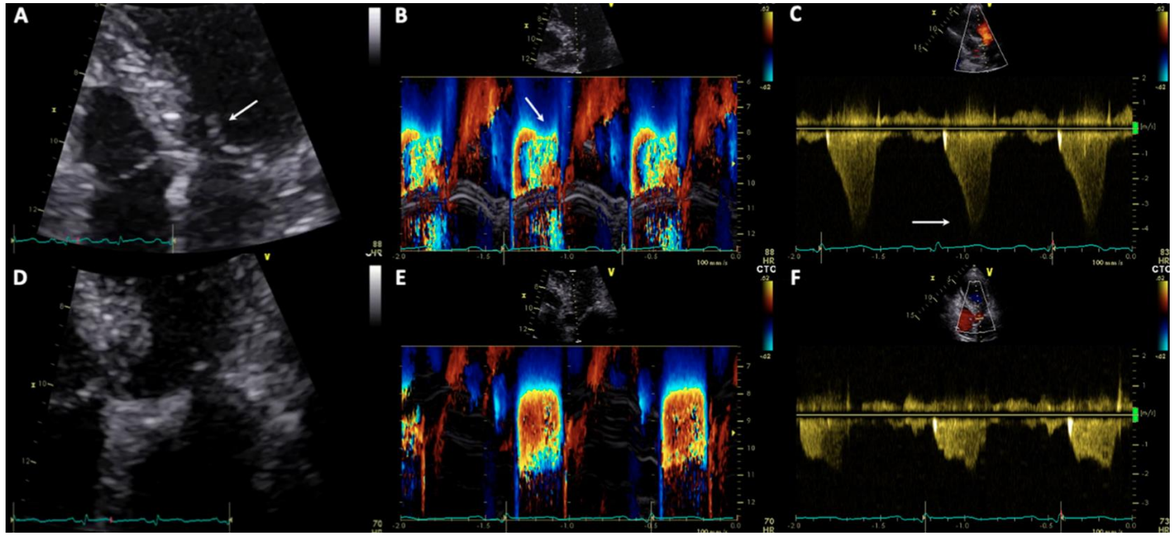
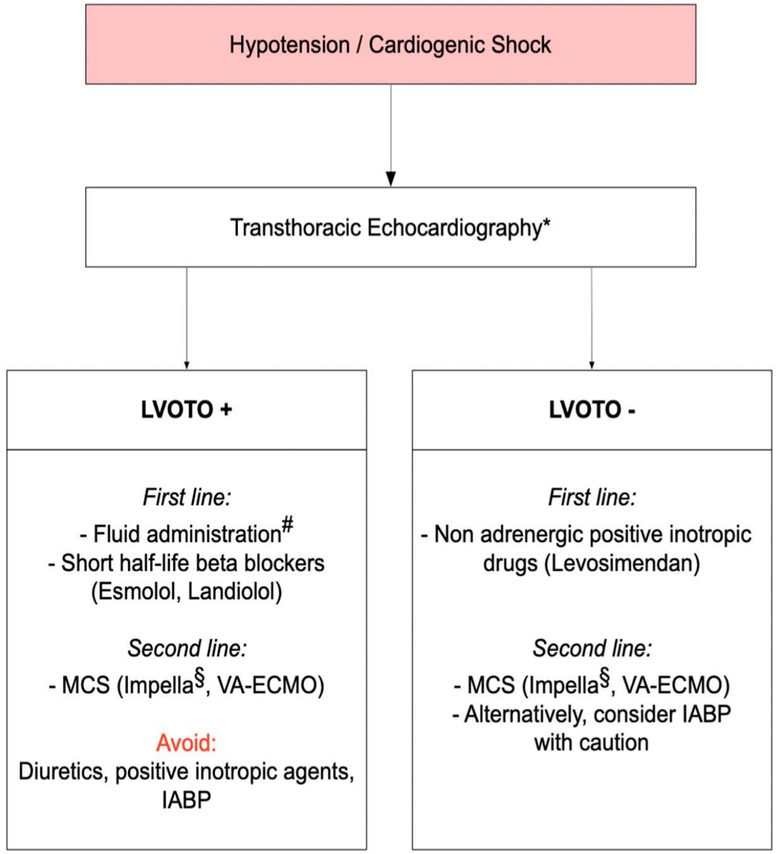
Review

Dynamic Left Intraventricular Obstruction Phenotype in Takotsubo Syndrome

Davide Di Vece [1], Angelo Silverio [2], Michele Bellino [2], Gennaro Galasso [2], Carmine Vecchione [2,3], Giovanni La Canna [4] and Rodolfo Citro [2,5,*,†]



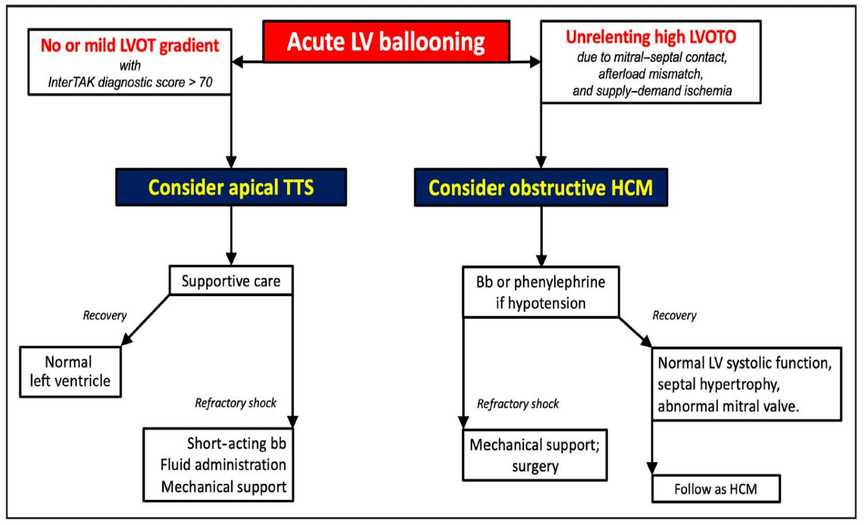


Journal of the American Heart Association

CONTEMPORARY REVIEW

Obstructive Hypertrophic Cardiomyopathy and Takotsubo Syndrome: How to Deal With Left Ventricular Ballooning?

Rodolfo Citro, MD, PhD; Michele Bellino, MD; Elisa Merli, MD, PhD; Davide Di Vece, MD; Mark V. Sherrid, MD



Mechanisms of Acute Mitral Regurgitation in Patients With Takotsubo Cardiomyopathy

An Echocardiographic Study

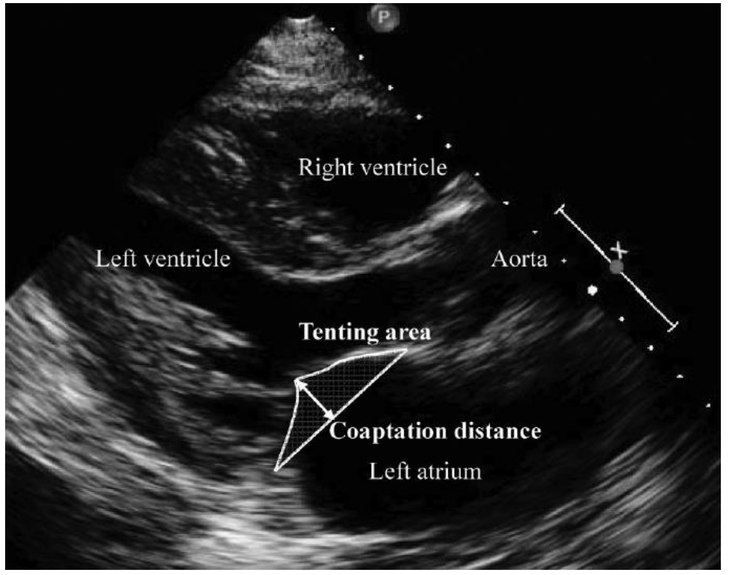
Masaki Izumo, MD, PhD; Smruti Nalawadi, MD; Maiko Shiota, MD; Jayanta Das, MD; Suhail Dohad, MD; Eiji Kuwahara, MD, PhD; Yoko Fukuoka, MD; Robert J. Siegel, MD; Takahiro Shiota, MD, PhD

Background—Recent studies have suggested acute mitral regurgitation (MR) as a potentially serious complication of takotsubo cardiomyopathy (TTC); however, the mechanism of acute MR in TTC remains unclear. The aim of this study was to elucidate the mechanisms of acute MR in patients with TTC.

Methods and Results—Echocardiography was used to assess the mitral valve and left ventricular outflow tract (LVOT) pressure gradient in 47 patients with TTC confirmed by coronary angiography and left ventriculography. Mitral valve assessment included coaptation distance, tenting area at mid systole in the long-axis view, and systolic anterior motion of the mitral valve (SAM). Of the study patients, 12 (25.5%) had significant (moderate or severe) acute MR. In patients with acute MR versus those without acute MR, we found lower ejection fraction (31.3±6.2% versus 41.5±10.6%, $P=0.001$) and higher systolic pulmonary artery pressure (49.3±7.4 versus 35.5±8.9 mm Hg, $P<0.001$). Moreover, 6 of the 12 patients with acute MR had SAM, with peak LVOT pressure gradient >20 mm Hg (average peak LVOT pressure gradient, 81.3±35.8 mm Hg). The remaining 6 patients with acute MR revealed significantly greater mitral valve coaptation distance (10.9±1.6 versus 7.8±1.4 mm, $P<0.001$) and tenting area (2.1±0.4 versus 0.95±0.25 cm^2, $P<0.001$) than those without acute MR. A multivariate analysis revealed that SAM and tenting area were independent predictors of acute MR in patients with TTC (all $P<0.001$).

Conclusions—SAM and tethering of the mitral valve are independent mechanisms with differing pathophysiology that can lead to acute MR in patients with TTC. **(*Circ Cardiovasc Imaging*. 2011;4:392-398.)**

Key Words: cardiomyopathy ■ mitral valve insufficiency ■ echocardiography



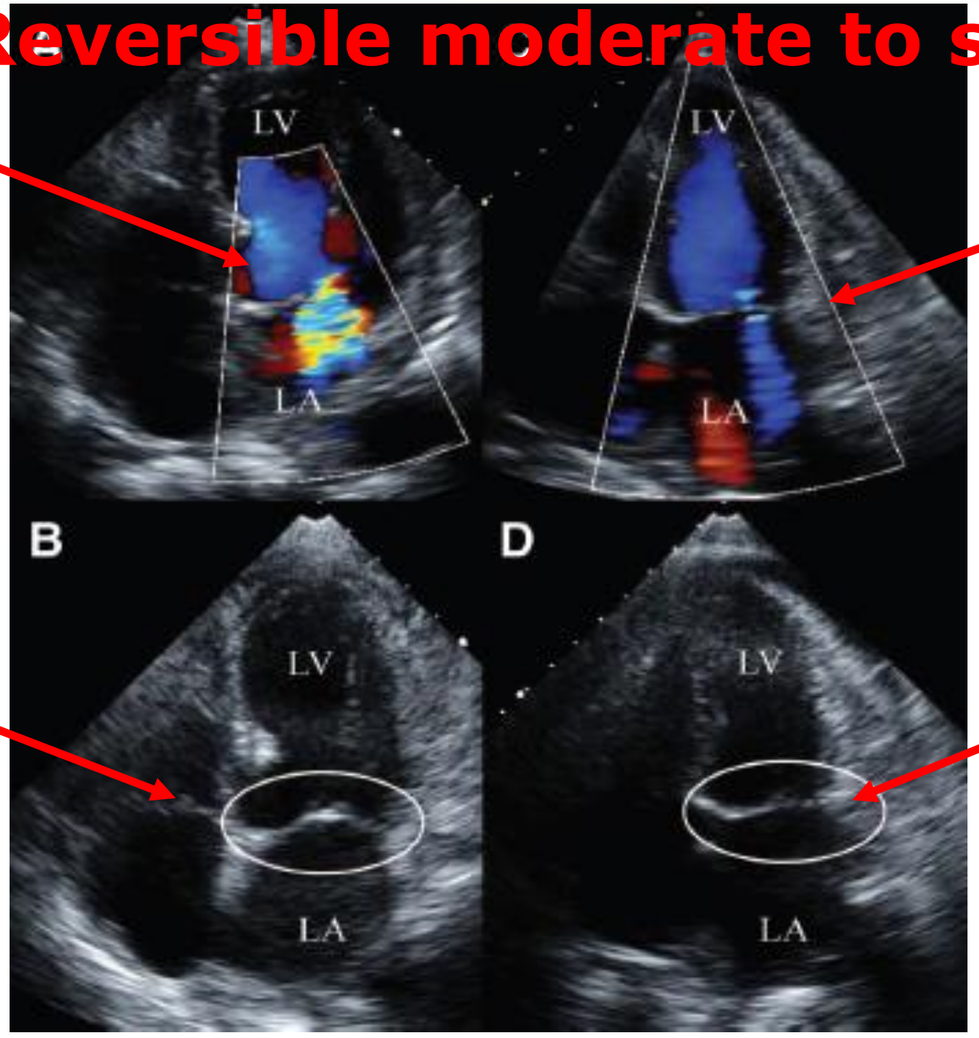
TTS: Reversible moderate to severe MR

Severe MR at presentation

Mild MR at follow-up

Apical displacement (tenting area)

No tenting area at follow-up



Izumo M Circ Cardiovasc Imaging 2011

CONCLUSION

Echocardiography should be systematically performed in TTS patients to identify whether MR is present as well as to assess its mechanism.

SAM and tethering of the mitral valve are independent mechanisms with different pathophysiology that can lead to acute MR in patients with TTS.

Being acute MR in TTS reversible despite current guidelines recommend mitral valve surgery in symptomatic unstable patients with severe acute MR; aggressive medical treatment or MCS according to the different etiologic mechanism should be preferred