International Journal of Cardiology 288 (2019) 1–4

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Evaluation of ventriculo-arterial coupling in ST elevation myocardial infarction with left ventricular dysfunction treated with levosimendan

Paolo Trambaiolo [a,*], Pietro Bertini [b], Nunzia Borrelli [c], Marco Poli [a], Silvio Romano [c], Giuseppe Ferraiuolo [a], Maria Penco [c], Fabio Guarracino [b]

[a] ICCU, Sandro Pertini Hospital, Roma, Italy
[b] Department of Anesthesia and Critical Care Medicine, Cardiothoracic and Vascular Anesthesia and Intensive Care Unit, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy
[c] Cardiology Dept, L'Aquila University, Italy

ARTICLE INFO

Article history:
Received 2 March 2019
Received in revised form 10 April 2019
Accepted 16 April 2019
Available online 17 April 2019

Keywords:
Ventriculo-arterial coupling
Elastance
Pathophysiology
Echocardiography
Levosimendan
Tailored approach

ABSTRACT

Background: Acute heart failure (AHF) after ST-segment elevation myocardial infarction (STEMI) is usually treated with inotropic support or vasoactive medications.
In this study, we aimed at investigating the role of levosimendan on cardiovascular determinants of contractility and afterload in patients with AHF following STEMI treated with percutaneous coronary intervention (PCI).
Methods: Forty-eight consecutive STEMI patients were retrospectively enrolled. Non-invasive assessment of left ventricular elastance (Ees) and arterial elastance (Ea) and their relationship, ventriculo-arterial coupling (VAC) was performed before and after levosimendan infusion.
Results: After infusion of levosimendan a significant increase in SV was detected in all patients (from 48 ± 17 to 60 ± 21 ml, $p < 0.001$). VAC slightly decreased from 1.74 ± 0.8 to 1.66 ± 0.7 (p = NS) as a result of a profound reduction in arterial elastance (Ea 2.34 ± 1.09 to 1.74 ± 0.5 mm Hg/ml, $p < 0.001$) and in ventricular elastance (Ees 1.57 ± 0.12 to 1.24 ± 0.09 mm Hg/ml, $p = 0.021$). Ejection fraction (EF) (from 0.29 ± 0.1 to 0.32 ± 0.1, $p < 0.01$) and WMSI, (from 2.16 ± 0.47 to 2.05 ± 0.54, $p < 0.05$) also, significantly improved.
Finally, baseline VAC was able to predict the use of norepinephrine (NE) and early and one-year mortality of patients treated.
Conclusion: In STEMI patients with AHF the use of levosimendan significantly increases stroke volume after 24-hour treatment through Ea reduction. Baseline VAC seemed to predict early and late mortality and early and prolonged use of NE, however, this needs to be tested in larger series of patients and multivariate adjustments for other prognostic predictors.

1. Introduction

Acute heart failure after a ST-segment elevation myocardial infarction (STEMI) is commonly treated pharmacologically with intravenous positive inotropic agents and/or vasopressors. Beta-adrenergic agents increase stroke volume (SV) and cardiac output (CO) stimulating adenylate cyclase, with an increase in intracellular cyclic adenosine monophosphate production and calcium influx to myocytes. Phosphodiesterase inhibitors, like milrinone or enoximone, do the same by inhibiting cAMP degradation. Moreover, both beta-adrenergic agents and phosphodiesterase inhibitors increase cellular energy demands and oxygen consumption [1]. Differently, levosimendan is an "inodilator" with positive inotropic function and additional vasodilation activity [2,3]. It works by increasing calcium sensitivity of contractile proteins by binding cardiac troponin C (cTnC) in a calcium-dependent manner, thus increasing contractile force without impairing ventricular relaxation. On the other hand, levosimendan opens the adenosine triphosphate-sensitive potassium channels in vascular smooth muscle cells, inducing vasodilatation of systemic arterial resistance vessels and coronary arteries and systemic venous capacitance vessels [4]. Moreover, it also activates mitochondrial ATP-sensitive potassium channels in cardiomyocytes, an effect that seems to hold a key role in protecting myocardial and potentially other cell types against ischemia/reperfusion injury [5].

In animal studies, levosimendan seems to improve left ventricular (LV) diastolic function by increasing the rate of relaxation and thus reducing relaxation time and improving diastolic filling. Indeed, besides inotropy, levosimendan has a positive lusitropic effect on myocyte strips from human failing hearts, as it reduces relaxation time [6]. In a small randomized study in patients with advanced heart failure, levosimendan improves echocardiographic markers of abnormal LV diastolic function (transmitral flow patterns and mitral annulus velocities) [7]. Levosimendan has been shown to improve hemodynamics

* Corresponding author at: Viale Di Villa Pamphili 33, 00152 Roma, Italy.
E-mail address: paolo.trambaiolo@aslroma2.it (P. Trambaiolo).

https://doi.org/10.1016/j.ijcard.2019.04.052
0167-5273/

without a significant increase in oxygen consumption. Its use has been proposed in several settings including acute coronary syndrome [8].

Clinical assessment of response to inotropic treatment is usually based on SV and ejection fraction (EF) measurement. However, this approach does not consider the consequences of drug effects on myocardial oxygen consumption [9], whereas ventriculo-arterial coupling (VAC) [10–12], which reflects the relationship between myocardial contractility, expressed by ventricular elastance (Ees), and arterial afterload, expressed by arterial elastance (Ea) [13], better describes the efficiency of the cardiovascular system [14]. Such approach remained in the physiology lab for many years due to the need for invasive measurements. The validation of non-invasive assessment of Ees and Ea has brought VAC to the bedside and so made this pathophysiological approach feasible in the clinical setting [15,16].

As levosimendan use is recommended [17] in AHF patients and impacts on VAC [8] either in chronic heart failure (CHF) or in AHF, we aimed at investigating the early changes of VAC in STEMI patients with onset AHF receiving levosimendan.

2. Methods

After approval from Ethics committees for human biomedical research, 48 consecutive patients (92% male, mean age 64 ± 12 yrs) with AHF whose underlining etiology was STEMI with left ventricular (LV) dysfunction (EF < 40% [17]) admitted to the Cardiac Intensive Care Unit (CICU) between December 2015 and December 2016 were retrospectively enrolled.

We excluded patients younger than 18 years old, those with EF > 40% and patients with chronic renal failure under dialytic treatment.

Patient characteristics are displayed in Table 1. All patients underwent primary PTCA of the infarct-related artery according to ESC/AHA guidelines [18] and, subsequently, underwent levosimendan intravenous administration to treat severe LV dysfunction according to local protocol. Levosimendan (Simdax®, Orion Corporation, Finland) was administered according to the recommended standard dose for a continuous infusion of 0.1 mg/kg/min for 24 h. No bolus injection was used. Concomitant medications and procedures were left to the discretion of the attending physician. In patients with pre-existing cardiac disease, home therapy was continued throughout the CICU stay and prescribed upon discharge.

2.1. Echocardiographic monitoring

All patients underwent continuous electrocardiographic and invasive radial arterial blood pressure monitoring. We evaluated echocardiographic parameters basally on admittance to (CICU) and 24 h after the administration of levosimendan. VAC (Ea/Ees ratio) was obtained by a specifically implemented calculator (iElastance© - Apple iOS App) [19] designed for measuring non-invasive single beat end-systolic Ees according to Chen's method [15] and Ea as systolic blood pressure × 0.9 / SV (Fig. E1). The application is essentially a calculator specifically designed to use Chen's algorithm at the bedside.

Table 1
Baseline clinical characteristics. Data are expressed as mean ± SD, or as a percentage for categorical variables.

Age, years	68 ± 12
Male (%)	92
Heart rate, bpm	87 ± 20
Sinus rhythm (%)	81
Systolic blood pressure	112 ± 26
Diastolic blood pressure	67 ± 16
Smokers (%)	42
Diabetes mellitus (%)	38
Hypertension (%)	65
Dyslipidaemia (%)	44
Previous CAD (%)	40
Mechanical ventilation (%)	30
Norepinephrine (%)	15
ACE inhibitors/ARBs (%)	54
Beta blockers (%)	35
Calcium channels blockers (%)	8
Nitrates (%)	27
Other antihypertensive drugs (%)	6
Antiplatelet (%)	88
Oral anticoagulants (%)	54
Diuretics (%)	69
Hypolipidaemic drugs (%)	35

Measurements used are arterial blood pressure (both systolic and diastolic), SV, EF, total ejection time and pre-ejection time, as requested by the Chen's formula.

Normal value for VAC has been reported by Chantler et al. in 2012 and is 1 ± 0.36 [20].

We used the Doppler velocity-time integral (VTI) method for stroke volume assessment. (SV = LVOT area × LVOT VTI). LVOT area was measured in the parasternal long-axis view as: $LVOT^2 \times \pi / 4 = LVOT^2 \times 0.785$. The LVOT image was obtained with zoom option with a measurement "inner-edge to inner-edge" in mid-systole just adjacent to the leaflets. The LVOT velocity was recorded from the apical 5-chamber, with the sample volume positioned about 5 mm proximal to the aortic valve, approximately at the same location as the 2D measurements of LVOT. The closing click of the aortic valve or spectral broadening of the signal was seen when the sample volume was correctly positioned.

The biplane method of disks (modified Simpson's rule) was used as 2D method to assess LV EF.

The pre-ejection time and total systolic time were measured from the onset of the electrocardiographic QRS complex to the onset of ejection (onset of the aortic flow) and from the onset to the end of the aortic flow, respectively.

Lung B lines were detected bilaterally with phased array transducer. The presence of multiple lung B-lines was defined as at least three in a longitudinal scan between two ribs [21].

2.2. Statistical analysis

All demographic and clinical variables were expressed as mean ± SD. Categorical variables were expressed as number of subjects and percentages. Differences between baseline and treatment were compared by the Wilcoxon rank test for variables with non-normal distribution, by *t*-test for dependent samples for variables with normal distribution and by the chi-square test for dichotomous variables. Spearman's coefficient was used for the correlation analysis between stroke volume and Ea. For all analyses, a *p* value of <0.05 was considered significant. To obtain a statistical power of 0.8 with alpha 0.5 and 95% confidence intervals for the enrolment were calculated a priori that we would need 29 patients. Thus, we recruited over 40 patients to overcome any a priori un-estimated biases.

3. Results

Forty-eight patients (mean age 68 ± 12 years; 92% male) with STEMI and LV systolic dysfunction were enrolled in the study. All patients underwent primary PTCA of the culprit lesion. Fifteen of the enrolled patients required mechanical ventilation. Baseline characteristics and results after 24 h administration of levosimendan are shown in Table 2.

After infusion of levosimendan we detected a significant increase in SV when compared to baseline [from 48 (SD 17) to 60 (SD 21) ml, $p < 0.001$] in all patients treated. VAC slightly decreased from 1.74 (SD 0.8) to 1.66 (SD 0.7) (p = NS) as a result of a sharp reduction in arterial elastance [Ea (mm Hg/ml/m^2) 2.34 (1.09) to 1.74 (SD 0.5) mm Hg/ml/m^2, $p < 0.001$] and less in ventricular elastance [Ees (mm Hg/ml/m^2) from 1.57 (0.12) to 1.24 (0.09) mm Hg/ml/m^2, $p = 0.021$).

Heart rate remained substantially unchanged (from 87 ± 19 to 83 ± 19 bpm, p = NS), while ejection fraction (EF) and WMSI showed a significant improvement (from 0.29 (SD 0.1) to 0.32 (SD 0.1), $p < 0.01$, from 2.16 ± 0.47 to 2.05 ± 0.54, $p < 0.05$, respectively).

Our data show a statistically significant correlation between Ea reduction and SV increase (Fig. 1). Finally, after infusion of levosimendan we detected a significantly lower number of patients with lung B-lines (from 79 to 55%, $p < 0.01$).

Table 2
Effect of levosimendan on echocardiographic parameters.

	Baseline	24 h	*p*-Value
EF (0–1)	0.29 ± 0.1	0.32 ± 0.1	=0.03
Total ejection time (ms)	332 ± 53	319 ± 45	=0.10
Pre-ejection time (ms)	87 ± 29	74 ± 22	=0.02
Arterial elastance (mm Hg/ml/m^2)	2.34 ± 1.09	1.74 ± 0.5	<0.001
Ventricular elastance (mm Hg/ml/m^2)	1.57 ± 0.12	1.24 ± 0.09	=0.021
V-A coupling	1.74 ± 0.8	1.66 ± 0.7	=0.56
WMSI	2.16 ± 0.47	2.05 ± 0.54	=0.025
Stroke volume (ml)	48 ± 17	60 ± 21	<0.01
Aortic VTI	14.6 ± 4.6	18.2 ± 6.4	<0.001
B-lines (%)	79	55	<0.01

EF = ejection fraction, V-A coupling = ventriculo arterial coupling, WMSI = Wall Motion Score Index, VTI = velocity time integral.

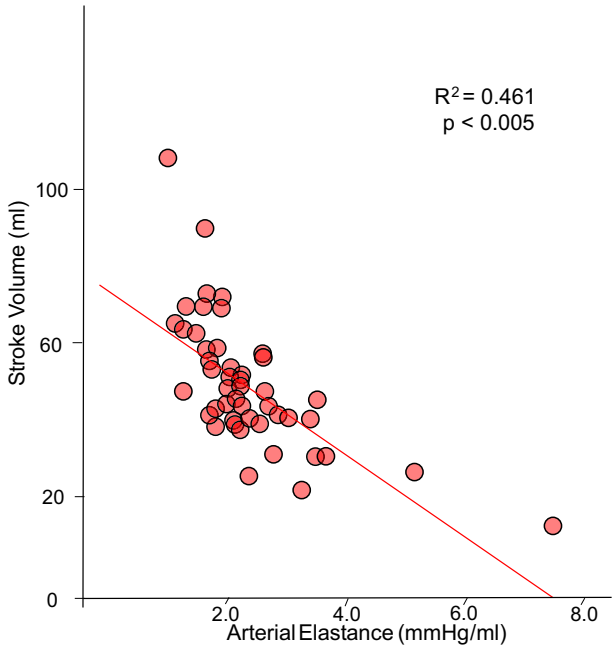

Fig. 1. Negative correlation between stroke volume (SV) and arterial elastance (Ea).

Baseline VAC could predict patients who would receive norepinephrine (2.45 ± 1.61) vs those who would not require it (1.62 ± 0.54), and showed the same performance to predict who would continue norepinephrine infusion after levosimendan application (2.24 ± 1.29 vs 1.17 ± 0.51).

Furthermore, baseline VAC was significantly higher in patients who died in the first 72 h after MI (9 patients, accounting for 19% early mortality): 2.53 ± 1.38 versus 1.56 ± 0.49 in patients who survived. ROC analysis demonstrated a sensitivity of 67% and a specificity of 82% to predict mortality for VAC > 1.99 (AUC = 0.786, $p = 0.008$) With respect to one year mortality (37.5%, 18 patients), VAC again seems to be a good predictor being higher in those who died (2.19 ± 1.05) vs the survivors (1.47 ± 0.48), ROC analysis showing a sensitivity of 66% and a specificity of 67% to predict late (1 year) mortality for VAC > 1.68 (AUC = 0.769, $p = 0.002$) (Fig. 2).

4. Discussion

Our data show that the patients who were admitted in the CICU with STEMI and LV dysfunction had a significant ventriculo-arterial decoupling associated with the observed impaired LV performance and increased Ea.

After 24 h we found that levosimendan significantly reduced both Ea and Ees so leading to a non-significant decrease in VAC. The reduction of ventricular elastance could be explained by the blunting of the well-known LV hypercontractility of normal segments in the early phase of STEMI, which could lead to overestimation of basal Ees [22].

The significant early increase of SV could be interpreted as the result of an improved VAC due to levosimendan effect on both the arterial system and the myocardium matching the afterload (Ea) to that LV contractility.

In the studied patients we observed a clear reduction in lung B-Lines; this is related to a reduction in lung congestion and could be also influenced by an improvement of diastolic dysfunction as previously reported [23].

Prediction analysis showed that in those patients requiring prolonged norepinephrine infusion basal VAC was significantly higher, based on this, as a low blood pressure could be the correct afterload for that dysfunctioning LV as demonstrated by non-invasive measurement of Ea/Ees ratio it might be inappropriate to use norepinephrine in order to increase arterial pressure without measuring VAC. However this has to be demonstrated in larger research studies.

Moreover, our data demonstrate the importance of the pathophysiological assessment of the ventriculo-arterial coupling in early and late prognosis: patients with baseline higher VAC values are the ones who died the most in the early and late (1 year) phase after MI.

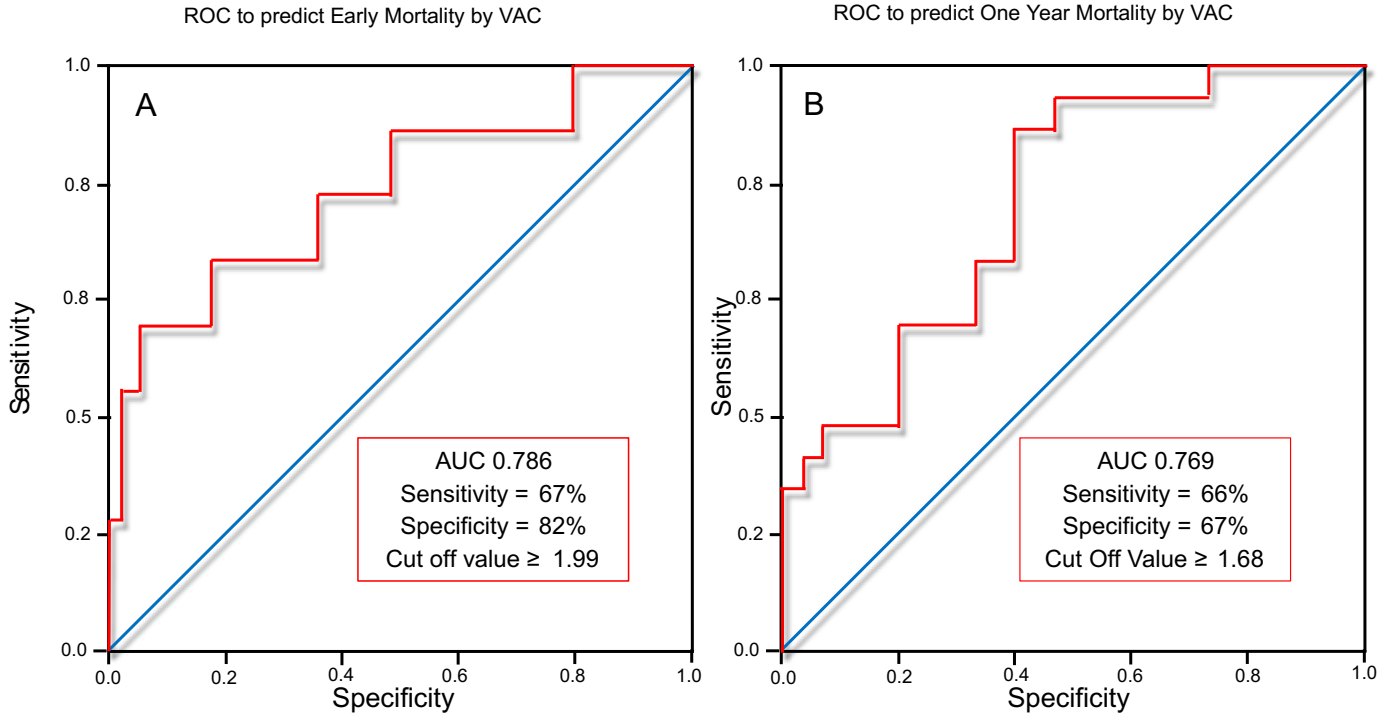

Fig. 2. ROC analysis showing prediction of early (Panel A) and one year mortality (Panel B) by ventriculo-arterial coupling (VAC) at the baseline.

4.1. Limitations

Our study has some limitations. First, it is a retrospective analysis of prospectively collected data of a limited number of patients. Second, the definition of Ea was simplified as Ea = end-systolic pressure / SV, which is routinely used as a valid surrogate. Third, non-invasive single beat analysis depends on the quality of the echocardiographic images. Attention was applied during echocardiography to avoid LV foreshortening, to precisely measure the LV outflow tract diameter, and to position the PW-Doppler sample volume. However, 2D echocardiography underestimates LV volume and for this reason we decided to consider only the SV obtained by Doppler method.

5. Conclusion

In this study, the use of levosimendan in STEMI patients with LV dysfunction significantly increased stroke volume after 24-hour treatment. The increase in stroke volume and the concomitant improvement of EF seems to be facilitated by Ea reduction, as demonstrated by a statistically significant correlation between Ea reduction and SV increase. VAC at the baseline seemed to predict early and late mortality and early and prolonged use of NE, however, this needs to be tested in larger series of patients and multivariate adjustments for other prognostic predictors.

Finally, a clear reduction in lung congestion was found, probably related to diastolic improvement.

These data show that in STEMI patients admitted with LV dysfunction a more pathophysiological approach might lead to a more personalised treatment. In the light of such results we speculate that the need for levosimendan should be based on an “echo-dynamic” approach which takes into account both myocardial contractility and arterial elastance.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.052.

Disclosures

Pietro Bertini is the author of software iElastance© - Apple iOS App.

References

[1] M. Bozhinovska, G. Taleska, A. Fabian, M. Sostaric, The role of levosimendan in patients with decreased left ventricular function undergoing cardiac surgery, Open Access Maced J. Med. Sci. 4 (2016) 510–516.
[2] P. Pollesello, Z. Papp, J.G. Papp, Calcium sensitizers: what have we learned over the last 25 years? Int. J. Cardiol. 203 (2016) 543–548.
[3] W.G. Toller, C. Stranz, Levosimendan, a new inotropic and vasodilator agent, Anesthesiology. 104 (2006) 556–569.
[4] J. Altenberger, F. Gustafsson, V.P. Harjola, K. Karason, D. Kindgen-Milles, M. Kivikko, et al., Levosimendan in acute and advanced heart failure: an appraisal of the clinical database and evaluation of its therapeutic applications, J. Cardiovasc. Pharmacol. 71 (2018) 129–136.
[5] D. Farmakis, J. Alvarez, T.B. Gal, D. Brito, F. Fedele, C. Fonseca, et al., Levosimendan beyond inotropy and acute heart failure: evidence of pleiotropic effects on the heart and other organs: an expert panel position paper, Int. J. Cardiol. 222 (2016) 303–312.
[6] G. Hasenfuss, B. Pieske, M. Castell, B. Kretschmann, L.S. Maier, H. Just, Influence of the novel inotropic agent levosimendan on isometric tension and calcium cycling in failing human myocardium, Circulation 98 (1998) 2141–2147.
[7] M. Okada, A. Suzuki, H. Yamawaki, Y. Hara, Levosimendan inhibits interleukin-1beta-induced cell migration and MMP-9 secretion in rat cardiac fibroblasts, Eur. J. Pharmacol. 718 (2013) 332–339.
[8] F. Guarracino, C. Cariello, A. Danella, L. Doroni, F. Lapolla, M. Stefani, et al., Effect of levosimendan on ventriculo-arterial coupling in patients with ischemic cardiomyopathy, Acta Anaesthesiol. Scand. 51 (2007) 1217–1224.
[9] F. Khalafbeigui, H. Suga, K. Sagawa, Left ventricular systolic pressure-volume area correlates with oxygen consumption, Am. J. Phys. 237 (1979) H566–H569.
[10] K. Sagawa, H. Suga, A.A. Shoukas, K.M. Bakalar, End-systolic pressure/volume ratio: a new index of ventricular contractility, Am. J. Cardiol. 40 (1977) 748–753.
[11] K. Sunagawa, W.L. Maughan, D. Burkhoff, K. Sagawa, Left ventricular interaction with arterial load studied in isolated canine ventricle, Am. J. Phys. 245 (1983) H773–H780.
[12] M.R. Starling, Left ventricular-arterial coupling relations in the normal human heart, Am. Heart J. 125 (1993) 1659–1666.
[13] R.P. Kelly, C.T. Ting, T.M. Yang, C.P. Liu, W.L. Maughan, M.S. Chang, et al., Effective arterial elastance as index of arterial vascular load in humans, Circulation. 86 (1992) 513–521.
[14] H. Suga, Total mechanical energy of a ventricle model and cardiac oxygen consumption, Am. J. Phys. 236 (1979) H498–H505.
[15] C.H. Chen, B. Fetics, E. Nevo, C.E. Rochitte, K.R. Chiou, P.A. Ding, et al., Noninvasive single-beat determination of left ventricular end-systolic elastance in humans, J. Am. Coll. Cardiol. 38 (2001) 2028–2034.
[16] F. Guarracino, B. Ferro, R. Baldassarri, P. Bertini, F. Forfori, C. Giannini, et al., Non invasive evaluation of cardiomechanics in patients undergoing MitrClip procedure, Cardiovasc. Ultrasound 11 (2013) 13.
[17] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G.F. Cleland, A.J.S. Coats, et al., 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, Rev. Esp. Cardiol. 69 (2016) 1167.
[18] Task Force on the Management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology, P.G. Steg, S.K. James, D. Atar, L.P. Badano, C. Blomstrom-Lundqvist, et al., ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, Eur. Heart J. 33 (2012) 2569–2619.
[19] P. Bertini, iElastance© - Apple iOS App, https://itunes.apple.com/it/app/ielastance/id556528864 2019.
[20] P.D. Chantler, E.G. Lakatta, Arterial-ventricular coupling with aging and disease, Front. Physiol. 3 (2012) 90.
[21] F. Frassi, L. Gargani, S. Gligorova, Q. Ciampi, G. Mottola, E. Picano, Clinical and echocardiographic determinants of ultrasound lung comets, Eur. J. Echocardiogr. 8 (2007) 474–479.
[22] E. Rechavia, R. de Silva, P. Nihoyannopoulos, A.A. Lammertsma, T. Jones, A. Maseri, Hyperdynamic performance of remote myocardium in acute infarction. Correlation between regional contractile function and myocardial perfusion, Eur. Heart J. 16 (1995) 1845–1850.
[23] E. Picano, M.C. Scali, Q. Ciampi, D. Lichtenstein, Lung ultrasound for the cardiologist, JACC Cardiovasc. Imaging 11 (2018) 1692–1705.