Role of bedside-focused ultrasonographic evaluation in the critical patient: a case report

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ABSTRACT

We present the case report of an 80 years old woman with late post-traumatic (of low intensity without any immediate clinical alteration) onset of dysphnoea, chest pain and hypotension, in which bedside ultrasonography has been a very useful tool in immediate diagnostic definition (acute respiratory distress syndrome – ARDS due to multiple pulmonary contusions), considering and excluding all possible alternative diagnosis with the same clinical presentation, but also providing a "real time" evaluation of therapeutic regimen (hypovolemia versus excessive fluid embalance) and, last but not least, the chance to perform a close follow up of the ultrasonographic alterations (pleural effusion, signs of alveolar consolidation) pointed out at initial diagnosis. Moreworthly, it has been possible to identify the previous mentioned lesion before they had become evident to standard X-Ray chest evaluation.

SINTESI

Presentiamo il caso clinico di una donna di 80 anni che, in seguito ad un trauma di intensità lieve senza ripercussioni cliniche avvenuto qualche giorno addietro, presentava dispnea, dolore toracico ed ipotensione; l'ecografia eseguita "al letto" ha costitutito uno strumento molto utile nel conseguire una definizione diagnostica pressoché immediata (sindrome ARDS dovuta a contusioni polmonari), considerando ed escludendo nel contempo tutte le possibili diagnosi alternative con la medesima presentazione clinica; è stata possibile inoltre una valutazione in tempo reale dell'efficacia della terapia (ipovolemia versus sovraccarico volemico) e non ultimo per importanza, è stato eseguito un attento monitoraggio delle alterazioni ecografiche (versamento pleurico, segni di consolidamento polmonare) evidenziati alla diagnosi iniziale. Inoltre abbiamo rilevato che l'identificazione delle lesioni sopra menzionate è stato più precoce rispetto alla radiografia del torace standard.

Introduction

Bedside-focused ultrasonographic evaluation is a very useful tool, in addition to clinical examination, in order to define critical conditions eligible for a rapid diagnostic definition and an intensive therapeutic approach; herein we present a case report in which the coexistence of signs and symptoms common to different pathological conditions leads us to formulate multiple diagnostic hypotheses and to quickly resolve them with the aim of bedside-focused ultrasonography evaluation.

Case report

An 80-year-old caucasian woman was admitted to our hospital because of progressive dysphnea and rapid onset of chest pain – defined by "borderline" features suggestive of acute coronary syndrome[1] – but absent of fever, cough and any other sympthoms. Her past medical history was unremarkable except for chronic haemodinamically stable atrial fibrillation not requiring antiarrhythmic drugs but treated with anticoagulant therapy. She referred of recent left thoracic trauma five days before and presented signs of wall thoracic ecchimosis. Upon clinical examination, airflow was adequate but she presented severe hypotension (80/50 mmHg), heart rate 110/min, Glascow Coma Scale 15/15, and dysphnea (respiratory rate 32/min, SO_2 80% with FiO_2 0.21). Clinical, rectal and neurological examinations were normal without any evidence of gastrointestinal blood loss. Axillary temperature was 36.5°C, while her electrocardiogram revealed atrial fibrillation with normal ventricular rate and morphology. An arterial blood gas specimen (performed with Radiometer-ABL) revealed pH 7.35, PO_2 35 mmHg, PCO_2 48 mmHg, HCO_3 25 mEq/l with calculated PaO_2/FiO_2 = 166 (with haemoglobin 9.0 mg/dl and lactate 2.6 mmol/l). Chest X-Ray examination did not detect any pathological findings in the lungs and ribs. Clinical suspicion of pulmonary embolism was unlikely according to Well's Score and Ginevra score. Reservoir 100% oxygen supply and fluid challenge with normal isotonic saline at a rate of 250 ml/30 minutes were started and a vescical catetherism was performed in order to monitor diuresis. Awaiting emocromocitometric and other clinical biochemical examinations, we performed bedside-focused emergency ultrasonography evaluation. Lack of collapse of inferior vena cava with inspiration ruled out a hypovolemic condition (Figures 1 and 2), the presence of free peritoneal fluid was excluded, while cardiac transtoracic exploration of the heart excluded acute left ventricular failure, cardiac tamponade and acute right ventricular dilatation due to severe pulmonary hypertension; chest ultrasonography detected a non-omogeneus pattern of multiple B-lines arising from the pleural line, mostly in the left emithorax, with confluent consolidations zone and the presence of focal signs of parenchymal distruption with localized pleural effusion

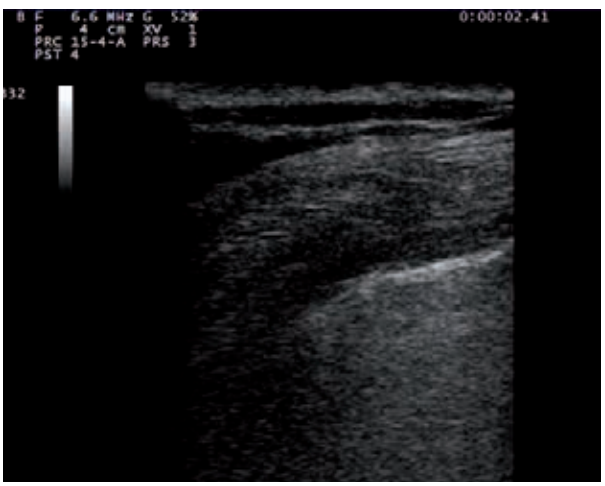

Fig. 1 - Ultrasonography at admission.

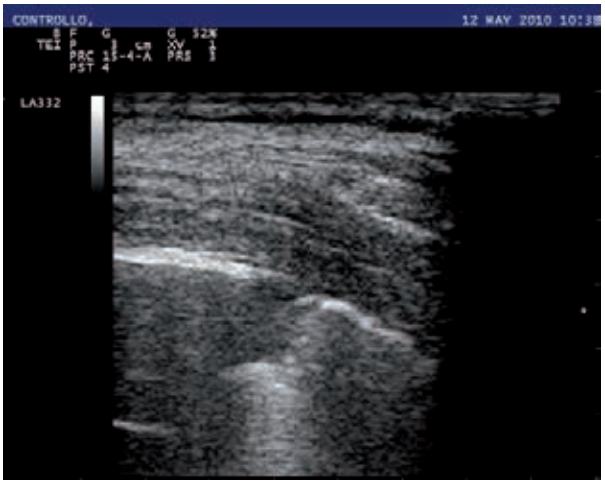

Fig. 2 - Ultrasonography after three days.

(Figures 3, 4 and 5), which is a picture of classic alveolar-interstitial syndrome pattern according to applying classic guidelines[2], while an alternative diagnosis of cardiogenic pulmonary edema, pneumothorax, pericardial tamponade and pulmonary embolism was excluded.
Hematologic and chemistry laboratory values were: Ht 29,5%, Hb 92 g/l, white cell count 14,000/mm^3, neutrophilis 12,700/mm^3, platelet count 133,000/mm^3, INR 2.45, fibrinogen 2.75 g/l, D-Dimer 142 µg/ml, total bilirubin 1,32 mg/dl, direct bilirubin 0,3 mg/dl, albumin 2.9 g/l, ferritin 45 mg/dl, CRP 11 mg/l. Conventional I-troponin monitoring was normal as well as myoglobin (Table 1).
The main diagnostic hypothesis was consistent with "acute respiratory distress syndrome" (ARDS) secondary to a pulmonary contusion. Therefore the diagnosis was confirmed by a thorax and abdominal contrasted-enhanced computed tomography

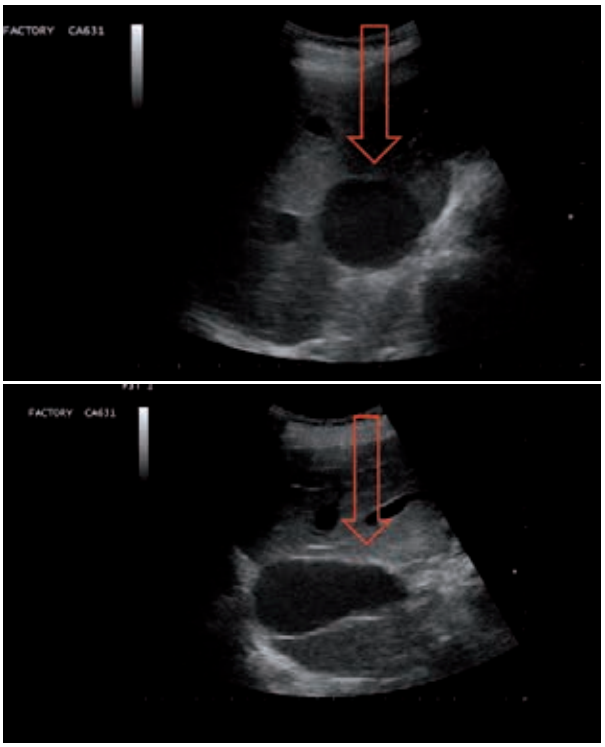

Fig. 3, 4 - A dilatated IVC (IVC diameter > 20 mm) roules out hypovolemia; IVC is measured in the sub-xiphiod space in the long and trasversal axis, using the liver as a sonographic window.

Table 1
Hematologic and chemistry laboratory values.

	Admission	III day	2 weeks after
Hb (g/l)	92	60	104
MCV (fl)	71	76	78
White cell (per mm)	14000	2800	9600
Platelet count (per mm)	133000	80000	204000
Fibrinogen (g/l)	2,75	3,93	3,2
Total bilirubin (mg/dl)	1,32	1,34	0,98

scan, which revealed minimal bilateral pleural effusion with multiple parenchimal infiltrates compatible with post-contusive consolidations and hematoma of thoracic wall.
A serious anemia and thromocytopenia have subsequently there occurred due to excessive platelet consumption, thus the patient received transfusion with two packed red cell units.
The ultrasosnographic findings described above underwent to close follow up and correlation with clinical condition and therapy's adjustement:
- After first three days of fluid therapy at rate of 60-80 ml /h un-

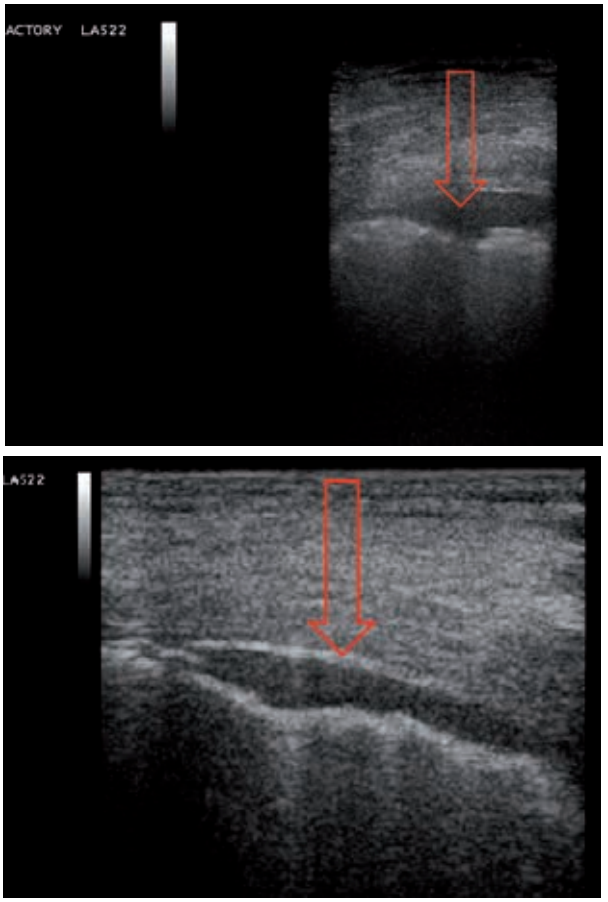

Fig. 5, 6 - Ultrasonographic pattern of parenchymal lung consolidation; hypoechoic subpleural focal images with or without pleural line gap, either isolated or multiple, appear as hypoechoic pleural-based focal images allowing ultrasound transmission, from which B-line-like artifacts arise, with confluent consolidations ("hepatization").

Table 2
Aetiological classification of main causes of shock.

Low cardiac output	High cardiac output
Hypovolemic	Septic
Cardiogenic	Anaphylactic
Extra-cardiac obstructive	Neurogenic

Table 3
Diagnostic tools with comparison in rapidity of execution and availability referring to most common clinical abnormalities.

Condition	Test	Rapid	Available
Hypovolemic			
• Gastrointestinal bleeding	Upper: NGT Lower: DRE	+++	+++
	Endoscopic	+	+
• Peritoneal bleeding/ AAA	Focused-US	+++	+/++
	CE-CT	+/++	++
• CVP low	Focused-US	+++	+/++
Cardiogenic			
• ACS	ECG	+++	+++
	I-troponin	+	+++
	Copeptin*	+++	?
• Structural hearth disease	Focused-US	+++	+/++
• Rhythm disturbance	ECG	+++	+++
• Aortic dissection/ rupture	CE-CT	+/++	++
Extra-cardiac obstructive			
• Pneumothorax	RX	++	+++
	Focused-US	+++	+/++
• Pleural effusion	RX	++	+++
	Focused-US	+++	+/++
• Cardiac tamponade	Focused-US	+++	+/++
• Pulmonary embolism	CE-CT	+/++	++
	Focused-US**	+++	+/++

*Not validated yet.
**Can exclude pulmonary embolism with emodinamical instability – useful for DVT.

til normalization of blood pressure, we could assist to a progressive lost of inspiratory inferior vena cava collapse (CVP exstimated 15-20 mmHg) with appearance of right lung B-lines; so diuretic therapy was started and anemia (also due to emodiluition) was corrected.
- In entire course of follow up no signs of left ventricular failure or pericardial effusion or free abdominal fluid were evident.
- Lung B-lines became less evident after four days from admission and extinguish at right lung after six days and at left lung after eight days.
- Signs of alveolar consolidation begun to decrease after five days and were not relievable after eleven days, while pleural effusion was not reliable after seventeen days (outward follow up visit).

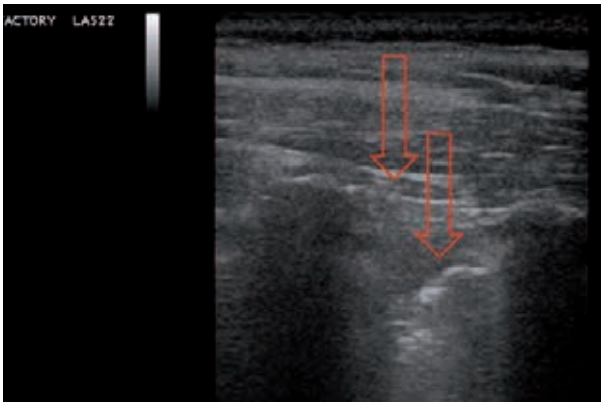

Fig. 7 - The presence of parenchymal disruption with localized pleural effusion.

Our patient was treated furthermore with oxygen, broad-spectrum antibiotics, low-molecular weight heparin (after suspension of dicumarolic therapy) and diuretics, obtaining a clinical and radiological remission in two weeks.
With close ultrasonography monitoring it has been possible to "titrate" fluid and diuretic therapy according to haemodinamic conditions, in particular after three-five days of admission. Also use of anticoagulant therapy (low molecular weight heparin) was safer because of the faculty of exclude free blood loss at any time.
Signs of alveolar consolidation became progressively less evident with course of antibiotic therapy(Figure 6), while resolution of "reactive" pleural effusion was slower.

Discussion

Rapid diagnosis and management of critical patients is strategic in the Emergency Department but hard in cases of unusual presentation or clinical abnormalities common to different pathologic conditions[2-5]. In our case report, careful anamnestic record, accurate physical examination and a few diagnostic tools – with the support of bedside-focused ultrasonography – allowed rapid diagnosis and effective treatment.
The reliability of bedside-focused ultrasonographic evaluation of the chest in the critical patient is demonstrated by the study in BLUE[6].
Dyspnea with chest pain and hypotension generally indicates

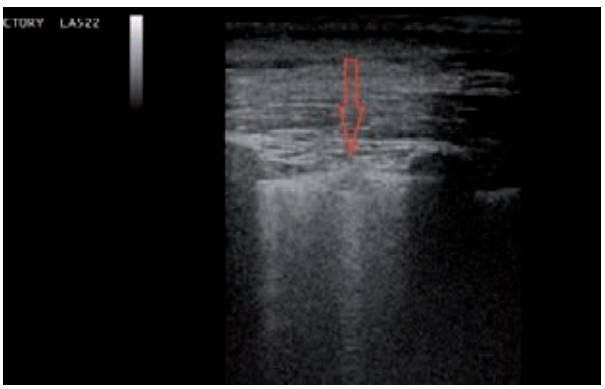

Fig. 8 - Ultrasound control showes size reduction of lesion.

shock due to low cardiac output (Table 2) and suggestive for hypovolemic (bleeding), cardiogenic (acute coronary syndrome or acute vascular injury), or extra-cardiac obstructive (occupation of pleural space, acute cardiac tamponade, massive pulmonary embolism) conditions.
While the use of a "pre-test probability" scoring system could rule out some pathological conditions (such as pulmonary embolism), the anamnestic recording of chest trauma and anticoagulant therapy associated with a normal ECG and the findings of moderate anemia and acute respiratory failure oriented our diagnostic pathway to a hypovolemic-post traumatic or pleuropulmonary acute condition (such as pneumothorax or emothorax or acute cardio-vascular rupture), despite a clinical cardiopulmonary examination without relevant pathologic findings (such as pleural effusion).
Rapidly performed bedside ultrasonography could easily exclude all pathological hypotheses listed above, thus confirming our diagnosis of ARDS secondary to pulmonary contusion[7-9].
In the Table 3 we list the most appropriate diagnostic tools with comparison in rapidity of execution and availability according to our diagnostic hypothesis.
Nowadays, largely standardized step-by-step protocols and guidelines assist every Emergency Departments team, in order to "focus on" only some clinical and anatomic points of interest, and to make it simple to perform and very reproducible.
FASTCRASH procedure (Focused Assessment Sonography for Trauma, Cardiac failure, Respiratory failure, Acute abdomen and Shock), introduced a few years back, provides rapid clinical and ultrasonographic evaluation of critically ill patients and delivers rapid and reliable results in order to identify the main problems and quickly (less than ten minutes) refer the patient to the most appropriate diagnostic/therapeutic procedure[2,9-11].
Ultrasonographic examination of chest is very useful in an emergency approach of dysphnea/respiratory failure and often provides a more accurate diagnosis of acute cardio-pulmonary disorders compared to standard chest X-Rays; it may be performed at the patient's bed and repeated frequently during follow up, thus avoiding unuseful patient transport and radiological exposition.
With a "targeted approach", recognition of pneumothorax, pleural effusion, parenchimal lung consolidation, diffuse interstitial infiltrates, pulmonary edema and other common conditions becomes very easy and accurate[11-13].

Conclusion

Lung contusion is a frequent clinical entity but often remains undiagnosed – especially upon first evaluation – because a diagnosis is unlikely with a visit and chest radiography[5,7,8]. Although TC is the gold standard for lung contusion diagnosis, it is expensive and subjects the patient to the risks of transport, contrast agent side effects and radiation and is therefore non-viable for the seriate monitoring of the patient. Various studies have demonstrated that chest ultrasonography can accurately detect lung contusion in blunt trauma victims: sensibility is 94.6%, specificy is 96.1%, positive and negative predictive values are 94.6% and 96.1% respectively and accuracy is 95%[8].
In an emergency situation, a traumatized patient showing signs of shock and acute respiratory deficiency poses a challenge for an ER doctor whose quick and precise diagnosis is needed in order to ensure an effective treatment. Pneumothorax and pleural effusion are accessible to ultrasound; information obtained from lung, cardiac, venous and abdominal analysis provides a bedside visual approach to the critically ill[9,14-16]; according to FASTCRASH method (Focused Abdominal Sonography for Trauma, Cardiac arrest / failure, Respiratory arrest / failure, Acute abdomen and Shock) which constitutes an important tool and leads the intensivist to a more confident management and follow up of critically ill patients[3].
In our case report, in compresence of thoracic traumatism and possible structural heart disease, it is difficult to distinguish cardiogenic responsibility of haemodynamic alteration and pulmonary direct injury from the responsibility of pain defense in the respiratory distress. Furthermore, in case of arterial hypotension associated, a distinction between hypovolemic form (iatrogenic or due to internal haemorrhage, especially in patient in anticoagulant therapy) and cardiogenic cause of hypotension itself became crucial.

Disclosures: all authors declare no conflict of interest.

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The use of the biomarker "copeptin" for the diagnosis of acute chest pain in the Emergency Department

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ABSTRACT

The aim of the study is to assess if copeptin, in combination with negative troponin, is able to accelerate the rule-out of AMI in patients with chest pain. The study was retrospectively conducted on three groups of patients selected according to their discharge diagnoses: patients with non-ST elevation myocardial infarction (NSTEMI), non-cardiac chest pain (NCCP), unstable angina (UA). Comparing the levels of copeptin, we found that the diagnosis of AMI is associated more often with copeptin positive values (> 14 pmol/l) than the diagnosis of NCCP and UA. However, about a quarter of our patients in which the combination of copeptin and troponin in the first blood sample was negative, the final diagnosis was AMI. According to our results, the combination of the two negative markers does not allow a safe rule out of AMI at time zero.

SINTESI

L'obiettivo dello studio è di verificare se la determinazione delle copeptina, in associazione alla negatività dei valori della troponina, è in grado di accelerare la diagnosi di esclusione di infarto miocardico acuto (IMA) in pazienti con dolore toracico.
Lo studio è stato condotto in modo retrospettivo su tre gruppi di pazienti selezionati in relazione alla loro diagnosi di dimissione: pazienti con infarto miocardico acuto senza sopraslivellamento del tratto ST (NSTEMI), dolore toracico non cardiaco (NCCP), angina instabile (UA).
Confrontando i livelli plasmatici di copeptina, abbiamo rilevato che la diagnosi di IMA è più frequentemente associata a valori di copeptina positivi (> 14 pmol/l) rispetto alla diagnosi di NCCP e UA. Comunque in circa un quarto dei nostri pazienti nei quali la determinazione di copeptina e della troponina nel primo campione ematico erano negativi, la diagnosi finale era di IMA. Questi dati mostrano che la combinazione negativa dei due biomarcatori non consente di escludere con sicurezza un IMA al tempo zero.
***Key words**: copeptin, biomarkers, chest pain, emergency room.*

Background

Nowadays chest pain is one of the most common causes leading to the Emergency Department (ED). It results in 5% of all visits[1]. The diseases that may occur with this symptom are different but, of all, cardiovascular diseases are those with the highest risk of death and, among cardiovascular diseases, acute coronary syndrome (ACS) is the most frequently involved. For this reason, among the many patients in the Emergency Department with chest pain, it is essential the early identification of those in whom the symptom is an expression of acute myocardial infarction (AMI) because these patients require timely and specific therapeutic approach.
Actually the diagnosis of acute myocardial infarction uses myocardial necrosis markers, primarily troponin (Tn), which is the gold standard uniformly approved and recommended by the guide lines[2]. On the other hand, it is known that, as expression of cell necrosis, Tn is not released immediately at the chest pain onset, but with a progressive rise according to the evolution of AMI, so it may still be negative when the patient arrives in the Emergency Department. In fact, the diagnostic protocol of patients with suspected acute coronary syndrome (ACS) provides serial samples at 0, 6, and 12 hours from the arrival to determine the so-called "curve" of Troponin and intervene if it becomes indicative of necrosis[3].
In case of failure diagnosis and improper discharge the short term mortality is high but, on the other hand, the systematic hospitalization of all patients with suspected ACS causes an unnecessary increase in costs. It seems clear, therefore, the need to search for a biomarker with pathophysiological background-independent cell necrosis which can be used in the ED to accelerate and improve the discrimination between chest pain due to an acute myocardial infarction from a chest pain of different origin.

Copeptin, as an endogenous marker of stress and with his immediate release after the acute event, it seems to have a role in the early exclusion of acute myocardial infarction[4]. It is the c-terminal part of the vasopressin prohormone and is secreted from the neurohipophysis in equimolar amounts with arginine-vasopressin (AVP)[5].
Numerous studies have shown that AVP plays an important role in endogenous stress response and thromboembolism, which are the basis of the pathophysiology of acute coronary syndrome[6,7]. However, the measurement of plasma vasopressin is a difficult task for several reasons: first of all, more than 90% of vasopressin in the circulation is bound to platelets, leading to an underestimation of the hormone levels[8]; secondly, it is quickly eliminated from the blood[9]; finally, vasopressin is unstable *in vitro*, even when stored at -20°C[10]. To overcome these problems it was introduced a method of indirect measurement of vasopressin, which consists in measuring a much more stable peptide like copeptin. There was no decay of copeptin immunoreactivity after its storage at -20°C[5].

Objectives

The aim of the study is to analyze cases of chest pain suspicious of acute coronary syndrome and whether the positivity of copeptin can support the final diagnosis of myocardial infarction, as demonstrated by the study of Reichlin[4]. From this study it was found that levels of copeptin < 14 pmol/l, in combination with negative troponin (≤ 0.03 ng/ml), would be able to exclude the diagnosis of myocardial infarction in the first sample with a diagnostic accuracy of 98%, more than troponin alone (86%). We propose to evaluate in the reality of an italian ED the reliability of the combination of troponin-copeptin to exclude the diagnosis of AMI with only a blood sample done at the arrival of the patient.

Table 1
Clinical characteristics of patients with NCCP and NSTEMI.

	NCCP (53 patients)	NSTEMI (43 patients)	p
Age (yrs)	56 (35-83)	74 (46-84)	**< 0.001**
Sex (male/ female)	32/21	31/13	NS
Systolic blood pressure (mmHg)	145 (106-210)	140 (110-200)	NS
Diastolic blood pressure (mmHg)	80 (65-110)	80 (60-110)	NS
Diabetes Mellitus (%)	6 (11.3%)	8 (18.6%)	NS
Hypertension (%)	18 (33.9%)	30 (69.7%)	**0.01**
Smoker (%)	14 (26.4%)	6 (13.9)	NS
Hyperlipidemia (%)	21 (39.6%)	19 (44.1%)	NS
Obesity (%)	16 (30.1%)	7 (16.2%)	NS
Family history of SCA (%) Missing for some patients	17 (68%)	23 (65.7%)	NS
Copeptin levels > 14 pmol/l (%)	**10 (18.8%)**	**19 (44.1%)**	**0.01**

Statistical tests used: Mann Whitney test: values are presented as median (range); Chi-quadro test (χ^2).

Methods

Study design and population

The study is conducted at the Emergency Department of Policlinico S. Orsola-Malpighi in Bologna. This is a retrospective study in which 122 patients were selected from a pool of 800 cases, collected from a previous prospective study on acute chest pain. The criteria for recruitment of this prospective study was patients over 35 years old and a chest pain onset within 24 hours, excluding traumatic cause. The 122 patients were selected based on their final diagnosis: 43 patients reported the final diagnosis of AMI NSTEMI, in order to test the sensitivity of copeptin; 53 had final diagnosis of non-cardiac chest pain (NCCP) to test the specificity of the marker. Finally, we have also selected a further group of 26 patients whose final diagnosis was found to be unstable angina (UA), in order to test whether the ischemia, when not accompanied by necrosis, is a stimulus to the release of copeptin. A written informed consent was obtained from all patients.

Routine clinical assessment

The patients followed a standard diagnostic and therapeutic protocol for assessing chest pain. Each patient was evaluated through an initial clinical diagnosis including history and physical examination, ECG, chest X-ray and a sample for routine blood tests, including troponin assay. The sample for the determination of copeptin was carried out in conjunction with the sample for troponin.

Adjudicated final diagnosis

The final diagnosis is defined as the diagnosis given at the moment of discharge from the hospital.
The diagnosis of infarction NSTEMI is defined, in accordance with the criteria ESC/ACC[2], as positivity of myocardial necrosis marker in association with symptoms of myocardial ischemia and/or ECG changes. The marker of necrosis of our reference is troponin T. It is indicated as positive, and therefore as an indicator of AMI, a value of troponin > 0.03 ng/ml in at least one of blood samples carried out at 0, 6, and 12 hours.
Instead, patients with final diagnosis of non-cardiac chest pain have troponin levels ≤ 0.03 ng/ml and no evidence of cardiac origin of the pain according to the subsequent investigations.
Finally, the term unstable angina indicates an angina that occurs at rest and has a sudden onset, sudden worsening, and stuttering recurrence over days and weeks. These patients have negative troponin values (≤ 0.03 ng/ml) because, although it is a pain of ischemic origin, this ischemia does not develop in to cardiac necrosis.

Biochemical analysis

The values of troponin T (TnT) were obtained by the immunoassay Elecsys® Troponin T Company Cobas. The blood sample was drawn through peripheral venous access and collected in tubes containing lithium heparin. All were performed with sterile technique.
Copeptin values were measured with the kit provided by the company copeptin Kryptor ® Brahms. Serum samples on which we have determined the markers were collected for the previous prospective study on acute chest pain and then cryopreserved until the time of our analysis.

Results

The characteristics of 96 patients diagnosed with NSTEMI and NCCP are shown in Table 1. Comparing the two groups, statistically significant variables are age and hypertension: in the group of NSTEMI, patients were older and among them hypertension was more frequent than in the group of NCCP. There were no significant differences in other cardiovascular risk factors.
In the NSTEMI group the determination of troponin in the first sample was positive (> 0.03 ng/ml) in 19 out of 43 patients (with values between 0.04 and 0.69). Obviously, in the group of NCCP troponin was negative. Regarding copeptin levels, we considered as cut-off of positivity 14 pmol/l, as shown in

Table 2
Frequency of cardiovascular risk factors in the NSTEMI group in relation to copeptin.

	Copeptin > 14 pmol/l (n = 19)	Copeptin ≤ 14 pmol/l (n = 24)	p
Hypertension	14	16	NS
Diabetes mellitus	6	2	NS
Smoker	7	16	NS
Hyperlipidemia	7	12	NS
Obesity	3	4	NS
Family history of SCA Missing for some patients	6/13	17/22	NS

Table 3

Specificity, sensitivity, positive predictive value and negative predictive value of copeptin, when associated with negative troponin values.

	NSTEMI	DTA (control group)
Test positive	10 (a)	10 (b)
Test negative	14 (c)	43 (d)
Specificity: d/(b+d)= 81.1%		VP+: a/(a+b)= 50.0%
Sensitivity: a/(a+c)= 41.6%		VP-: d/(d+c)= 75.4%

the work of Reichlin[4]. In the group of the NCCP, 10 out of 53 patients (18.8%) were positive, with values between 16.77 and 330, while among NSTEMI there were 19 positive cases out of 43 (44.1%), with values between 17.27 and 170.4. This difference in percentage was found to be statistically significant (p = 0.001).
In the NSTEMI group, copeptin expressed as median was 10.88 (range 4-170.4), while in the group of NCCP was 5.91 (range 4-330). We further divided the two groups by sex, but there were no significant differences regarding the prevalence of positive copeptin. We also assessed the frequency of cardiovascular risk factors in the NSTEMI group by dividing it into two subgroups with copeptin positive and negative, but no statistically significant differences were obtained (Table 2).

Table 4

Copeptin-troponin association in the NSTEMI group.

	Copeptin +	Copeptin -
Troponin +	10 (23%)	14 (33%)
Troponin -	9 (21%)	10 (23%)

Comparing the NSTEMI group with the group of NCCP as a control group we were able to obtain the data of sensitivity, specificity, positive predictive value and negative predictive value of copeptin when associated with negative troponin values (Table 3).
Crossing the data of troponin and copeptin in NSTEMI group, they resulted both positive in 21% of cases and both negative in 33%. In 21% copeptin was positive while troponin was negative and in the remaining percentage (23%) copeptin was negative while troponin was positive (Table 4).

Figure 1 shows the relationship between values of troponin and those of copeptin in the 96 patients with NSTEMI and NCCP. In the group of patients with NSTEMI and negative troponin determination of copeptin does not add significant information to the diagnosis because it is positive in only 10 out of 24 patients (41,6%).
Finally, we divided the group of NSTEMI into two subgroups according to the time between chest pain onset and arrival of the patient in the Emergency Department (Table 5). Contrary to what expected by an early marker, patients who presented

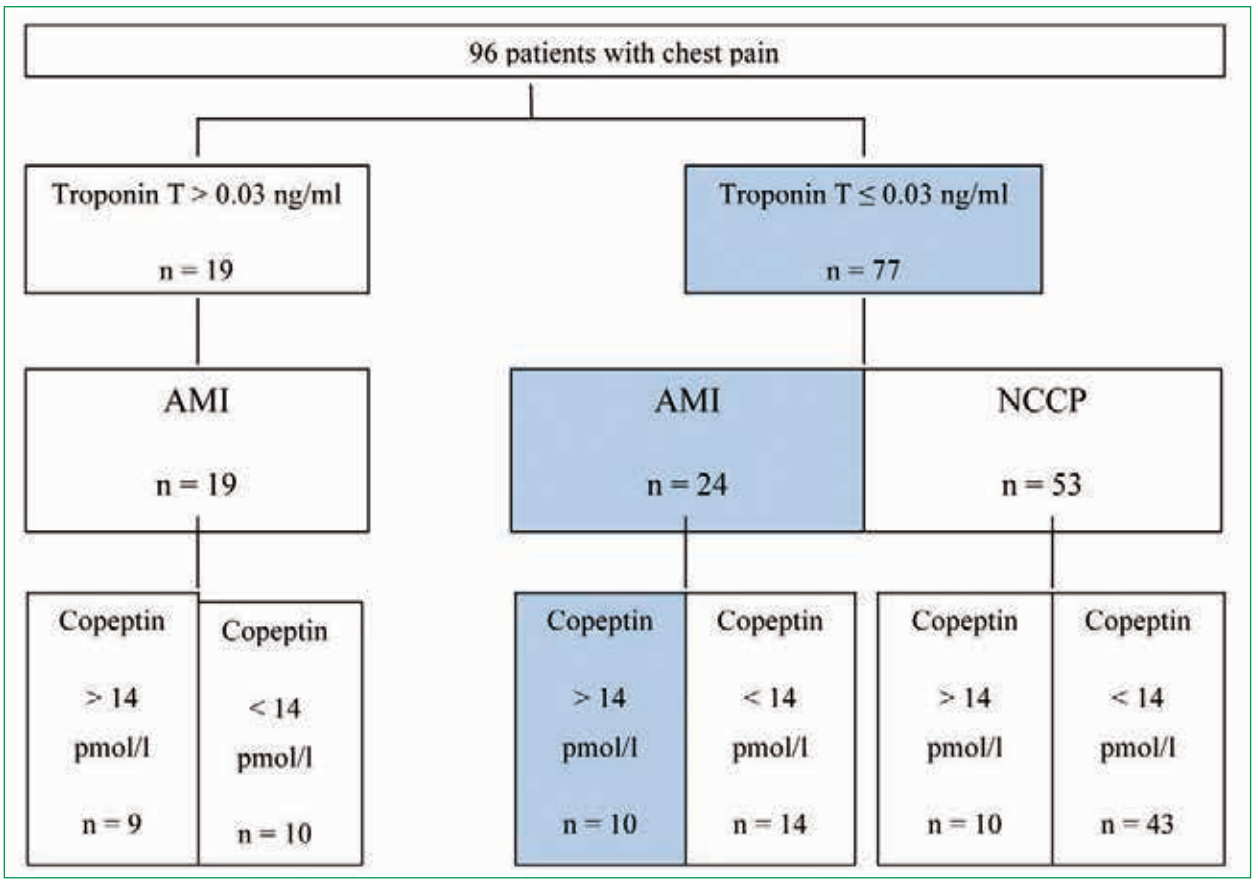

Fig. 1 - Copeptin levels according to discharge diagnosis and troponin T values.

Table 5

Copeptin levels in relation to time elapsed between chest pain onset and arrival in the ED.

	Time 0-4 hours	Time > 4 hours	p
Copeptin median (range)	9.445 (4-170.40)	13.57 (4-87.13)	0.206

within 4 hours of symptom onset had copeptin values lower than those that occurred later.
In the end, we compared the group of patients with unstable angina (UA) with NSTEMI group. In the UA only 3 out of 26 cases (11.5%) had positive copeptin levels, with values between 16.36 and 25.06, compared with 19 out of 43 cases (44.1%) in the NSTEMI group. Similarly to the comparison of DTA and NSTEMI, also in this case the difference in percentage was a statistically significant.

Discussion

The purpose of this study was to verify if the values of copeptin may be useful for rapid rule out of acute myocardial infarction. This retrospective study involved cases of acute myocardial infarction NSTEMI with a non-pathological ECG, since these are the cases in which serological markers of myocardial damage are of great importance in the decision making. As a control group the study involved consecutive cases in which it was excluded the diagnosis of SCA, cases of non-cardiac chest pain (NCCP).
According with expectations, we found that the diagnosis of NSTEMI was associated more often with positive values of copeptin than the diagnosis of NCCP.
In the NSTEMI group, we also assessed the time between the chest pain onset and presentation of the patient in the Emergency Department. Our data showed that patients that arrived within the first 4 hours of symptom onset and with a negative troponin had copeptin values not higher than patients that arrived later, as we would have expected from a marker of early diagnosis.
In more than a quarter of the cases (33%) in which the combination of copeptin and troponin was negative, the final diagnosis was NSTEMI. This percentage is too large to say that the combination of the two negative markers allows a safe rule-out of acute myocardial infarction. The negative predictive value of copeptin in association with negative troponin was 75.4%. It differs from the negative predictive value of 99.7% found by Reichlin, which guaranteed a rapid and reliable rule out of AMI, extremely useful in terms of clinical management.
Finally, comparing the group with NSTEMI and the UA group, the difference in the percentage of positive copeptin cases puts the group of UA at the same level of the NCCP. This could mean that the ischemia, in absence of cardiac necrosis, is not a sufficient stimulus to the release of the marker.
In summary, although copeptin is more frequently positive (> 14 pmol/l) in the NSTEMI group with a statistically significant difference compared with the control group (NCCP) and compared to the UA, this information can not be useful in terms of clinical management.

Study limitations

The main limitation of our study is the small number of patients: only 43 patients with diagnosis of AMI and only 53 cases of non-cardiac chest pain for comparison.
Secondly, what might explain the discrepancy of our data with those of Reichlin could be the patient selection. Reichlin included in his study patients with symptoms suggestive of ACS which means by definition patients with Chest Pain Score > 4. In our study we included cases of chest pain less selected from the clinical point of view in order to test the usefulness of the marker in a larger variability of patients with this symptom, characteristic of the Italian Emergency Department. This might explain the high copeptin values found in the group of NCCP. In fact, they might be due to diseases different from myocardial infarction, but presented with acute chest pain and caused the rise in endogenous marker of stress (for example: bronchopneumonia). However, it remains to explore the low negative predictive value found with our cases (75.4%). With further study we could analyze the proportion of patients with negative troponin and copeptin who received a final diagnosis of NSTEMI to understand what factors have affected the thesis on the rapid and safe rule out of AMI.

Conclusions

In conclusion, we can say, according to our results, that copeptin is involved in the endogenous stress response triggered by an acute myocardial infarction, but has no distinctive features wich make it useful in the clinical management of chest pain.

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Sanguinamento da rottura di varici da un sito raro nell'ipertensione portale

Diagnosi differenziale con le cause di shock ipovolemico acuto in emergenza

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SINTESI

L'ipertensione portale è l'aumento della pressione nel sistema venoso portale, il quale riceve circa 1500 ml/m di sangue proveniente dall'intestino tenue, dal colon, dalla milza e dal pancreas. Un'ostruzione del flusso o un aumento delle resistenze a qualsiasi livello dell'albero portale comporta l'aumento della pressione nel sistema e la formazione di circoli collaterali tra la vena porta e le vene cave superiore e inferiore, creando le condizioni per la nascita di varici in tutto il sistema[1]. Viene presentato, di seguito, il caso di una donna con cirrosi epatica scompensata, voluminosa ascite e sanguinamento da rottura di varici a livello dell'asse splenico che ha posto, sin dall'inizio, per come si è presentato, il problema di diagnosi differenziale con altre cause di shock ipovolemico. Tale caso si è concluso con l'exitus della paziente.

Caso clinico

Una donna di 66 anni viene trasportata dal 118 al nostro DEA in stato di shock e con un violento dolore in regione dorso-lombare sinistra insorto improvvisamente al proprio domicilio. La paziente, sofferente di cirrosi epatica con voluminosa ascite e trombosi della vena porta, era stata sottoposta in passato a legatura di varici esofagee sanguinanti. Al domicilio della signora, l'equipe del 118 rileva un GCS di 15 ed un grave stato ipotensivo con pressione arteriosa non rilevabile. Al suo arrivo al DEA, la paziente è pallida, agitata, lamenta un forte dolore in sede dorso-lombare di sinistra. Non si individua la pressione arteriosa ed il polso carotideo è flebile. I parametri laboratoristici sono:

- GB 7,7 x 10^3
- GR 3,58 x 10^6
- HB 10,2 g/dl
- HCT 30,4%
- PLT 71 x 10^3
- INR 1,05
- PT 11 sec
- PTT 30 sec
- Glicemia 65 mg/dl
- Creatinina 1,04 mg/dl
- K 4.00 mmol/l
- NA 142 mmol/l

L'ECG evidenzia un ritmo sinusale di 125 b/m, BBDX-incompleto, EAS. Il GCS è di 12 con peggioramento delle condizioni generali. Si ha obnubilamento di sensorio e gasping; il GCS ha uno score di 7 per cui si procede all'intubazione. Si somministrano due fiale di dopamina in 250 cc di fisiologica e una sacca di sangue gruppo 0 (GRC). Si rileva un primo episodio di asistolia, quindi si procede con un ciclo di MCE, alla somministrazione di una fiala di adrenalina ed una di atropina ev, con la ricomparsa di un ritmo organizzato caratterizzato da complessi stretti e regolari. A questo punto una puntura esplorativa dell'addome mette in evidenza sangue libero in addome con liquido ascitico. Si invia in radiologia la paziente per TC toraco-addominale con mdc il cui esito rileva lo spandimento libero addominale da rottura delle vene ectasiche a livello dell'ilo splenico e diffuso versamento ascitico-ematico (Figura 1).
Date le precarie condizioni emodinamiche della paziente e il rifiuto dei parenti a sottoporla ad intervento chirurgico di *shunts*, ella viene ricoverata nel reparto di rianimazione dove, in seguito ad altro episodio di asistolia, si constata l'exitus.

Discussione

La vena porta, che drena nel fegato il sangue del tratto addominale del sistema gastro-intestinale, della milza e del pancreas, è formata dall'unione della vena mesenterica superiore con la vena splenica (Figura 2).
A livello dell'ilo epatico si divide nei rami segmentali, a livello dei sinusoidi il sangue proveniente dalle venule portali terminali confluisce con il sangue dell'arteria epatica, per passare

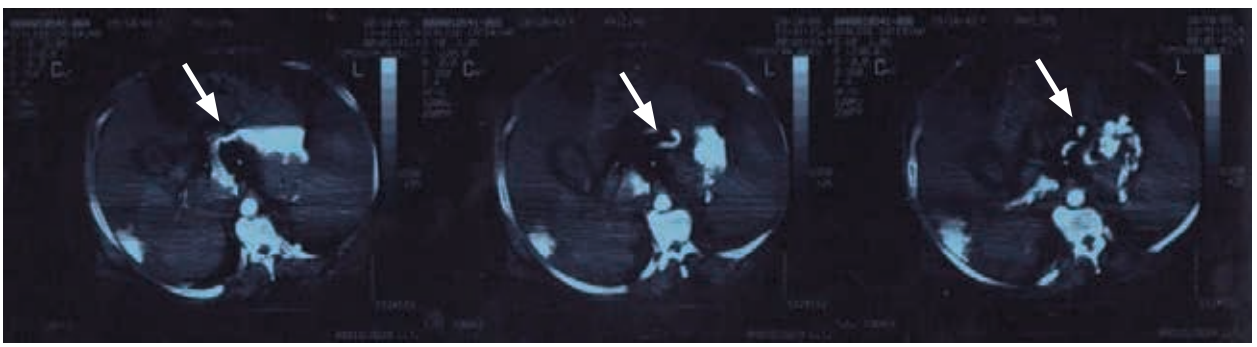

Fig. 1 - TC con mdc in sezioni assiali che evidenzia spandimento libero addominale da rottura varici ilo splenico, versamento ascitico.

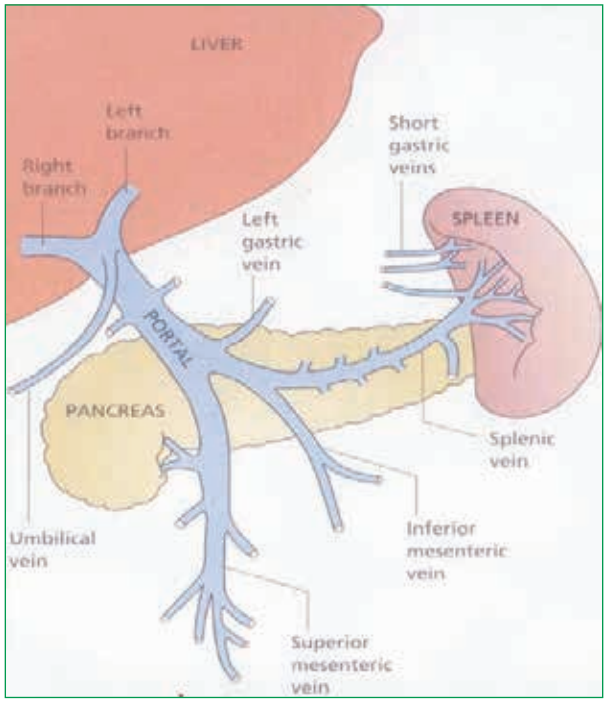

Fig. 2 – Sistema venoso portale.

poi nelle vene sovra epatiche, le quali drenano a loro volta nella vena cava inferiore. La vena porta fornisce circa il 70% del flusso ematico del fegato e circa il 60% del suo fabbisogno di O_2. La normale pressione portale è pari a 5-10 mmHg, quindi superiore alla pressione della vena cava inferiore di 4-5 mmHg (gradiente venoso portale). Valori superiori a 12 mmHg sono definiti come ipertensione portale[2]. Un aumento della stessa comporta la dilatazione dei circoli collaterali formatisi, la riduzione dello spessore della parete vascolare, l'aumento della tensione sulle pareti e infine la rottura del vaso. Le cause di ipertensione portale più frequenti sono:

- Pre-epatiche: trombosi vena porta e splenica, sindrome di Banti.
- Epatiche: tutte le cirrosi, schistosomiasi, fibrosi congenita.
- Post-epatiche: sindrome di Budd-Chiari, cardiomiopatia, pericardite, ostruzione vena cava inferiore, scompenso cardiaco severo.

L'ipertensione portale è asintomatica e i quadri clinici sono causati dalle sue complicanze, di cui le più importanti per drammaticità sono il sanguinamento acuto dalle varici esofagee e il sanguinamento dal fondo gastrico, quest'ultimo con un quadro meno drammatico, solo raramente il sanguinamento avviene da altre sedi. L'ematemesi di solito è massiva e senza dolore. La presenza di varici in un cirrotico è correlata strettamente con la severità della malattia epatica, espressa dallo score di Child-Pugh-Turcotte[3] (il 10-20% di pazienti Child A e il 70-80% di pazienti Child C sviluppa varici)[4]. La paziente rientrava in Child C. La mortalità in rapporto a ogni episodio emorragico è inferiore al 10% nelle cirrosi compensate in classe Child A, mentre sale a più del 70% in quelle in classe C. Il rischio di risanguinamento è elevato entro un anno dal primo episodio[5]. Il quadro clinico d'esordio del caso in esame ha posto il problema dell'inquadramento dello shock ipovolemico-emorragico complicato da asistolia. Secondo la classificazione dello shock ipovolemico da perdite ematiche nell'adulto[6], la paziente, non presentando pressione sistolica né diastolica, frequenza cardiaca > 120, frequenza respiratoria > 20/m, stato mentale non cosciente, rientrava in classe IV. Dinanzi a questo quadro clinico e tenendo conto della patologia di base, era d'obbligo una diagnosi differenziale tra tutte le cause di shock. Si è supposta la diagnosi di un addome acuto causato da un plausibile problema vascolare: la rottura di varice da un sito raro, come confermato dalla TC addome; la rottura di aneurisma dell'aorta addominale (AAA) o la dissecazione aortica addominale; l'infarto della mesenterica[7]. Si è supposta la diagnosi di una pancreatite necrotico-emorragica, di una perforazione di organo cavo, di una peritonite. Tutti quadri drammatici con gravi compromissioni emodinamiche che necessitavano di riscontro diagnostico. In conclusione, il caso presentato porta ad una evidente considerazione: più è severa la malattia di base, più aumenta il rischio di complicanze e il grado di mortalità[5,8]. Inoltre, nonostante l'ematemesi sia l'evento più frequente in corso di cirrosi epatica scompensata, in caso di shock ipovolemico da perdite ematiche sono da valutare anche altre possibili cause.

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