University „OVIDIUS" of Constanta

Physiology Department

CORELATIONS BETWEEN CLINICAL ASPECTS, NT-PROBNP VALUES AND OTHERS MYOCARDIAL CYTOLITIC ENZYMES IN PATIENTS WITH THORACIC TRAUMATHISMS

PHD THESIS SUMMARY

SCIENTIFIC LEADER
Prof. Dr. ION ILEANA

PHD STUDENT,
TASE CRISTINA RAMONA

CONSTANȚA

2008

TABLE OF CONTENTS

GENERAL PART

1.GENERAL PART

INTRODUTION

Hystorical researches about natriuretic peptides begings early in 1956 when studies that used electronic microspcopy shown that molecular granules similar with those seen in endocrine glands were found in atrial myiocardial cells. Grater discovery and hudge advance in the identification of atrial natriuretic peptide was made by Bold in 1981, who determined that by intravenous injection of that particular atrial extract he obtained a fast and powerfull reaction in rats. Secondary purification and a proper characterization of that biological factor made by numerous researchers lead to the discovery of the ANP factor in the period of 1983-1984. Future studies revealed the rest of natriuretic peptides family members by isolating two different molecular forms, named as : Brain Natriuretic Peptide BNP and C type Natriuretic Peptide CNP.

Even though BNP was initially isolated from cerebral material, studies proved that it's functional expression has a ventricular origin, cardiac myocites beying the major source of production for BNP and for eliberating it in the circulatory flow. In the blood stream, the active part of BNP hormone is composed by 32 AA fragments, completely separated by the N-terminal fragment of the pro-hormone, entitled NT-proBNP. This hormone is an important biomarker of classification of cardiac failure in all specific guidelines. At a time with chronic alteration of cardiac myocites, an over production and expression of natriuretic peptides has been proven.

Nowadays, important studies and researches have an eager to highlight the prognostic role of NT-proBNP in ventricular post traumatic failure. Mortality rates are second highest after head traumatic injury, which underlines the importance of initial management and evaluation criteria for life threatening risk patients .

2. EPIDEMIOLOGY OF TRAUMA

Worldwide , aproximativly 16.000 people die every day due to traumatic lesions (~ 5.8 milioane deaths/year), and the perspective for 2020 is a rise to iar estimările pentru anul 2020 arată o creștere pană la 8,4 million of deaths/year, Mortality being second highest after AIDS. The origin and severity of the pathology are in connection with the type and magnitude of the impact energy but also with the vulnerable state of the patient, most of them being male patients aged between 60-65 years old. Noticing the fact that politraumatic events are the result of high energy impact mechanisms, car crashes are at the top of the mortality lists in Europe and worldwide.

3. CARDIAC TRAUMA

Penetrating cardiothoracic lesions represent the cause of 25% of deaths the came in the first critical hours after a traumatic event, in 85% of them is needed a simple interventional procedure for treatment,being 85%, 15% requiring thoracotomy and the majority of them involving myocardial lesions or oh the great vessels. Non penetrating cardiac trauma is reported to have a 8 to 71% incidence of occurrence. Special attention is required in observing the clinical sings of shock alongside with ECG, cardiac tamponade, haemothorarax and identifying the top 6 imediat letal lesions:upper airwaves obstruction, tension pneumothorax, flail chest, cardiac tamponade, massive haemothorax, hypoxia, hypoventilation. 20% of the car accidents moratlity rates are due to non penetrating heart injury.

4. NATRIURETIC PEPTIDED WITH CARDIOVACULAR ROLE

Encountering ANP biomarker in 1981 by Bold and it's ventricular expression beautifully described by Nemer et al., followed by the descriptive role of BNP made the preogresion of cardiac endocrinology at that time and an innovating perspective for diagnosis of cardiac failure. Gentic studies of BNP and ANP and expression models implied a new set of regulatory pathways which confirm the role of this biomarkers in myocardial wall stress. Within dayly medical practice , enzymatic levels had a calitative implication as a marker of congestive heart failure stages and in the risk stratification of this group of patients, allowing also the screening of underling heart disease

There is no prognostic role determined by now for this enzyme applied in patients with acute heart damage as a cuase for traumatic events.

4.1 Biochemistry and pathophysiology of NT-proBNP

BNP human gene is located on chromosome 1 coding the 108 AA of the prohormone proBNP. In the bloodstream, BNP active hormone is composed by 32 AA parts beying separated from the N-terminal part of the pro hormone, NT-proBNP . the cleavage and specific location of pro BNP it is still on reaserch.

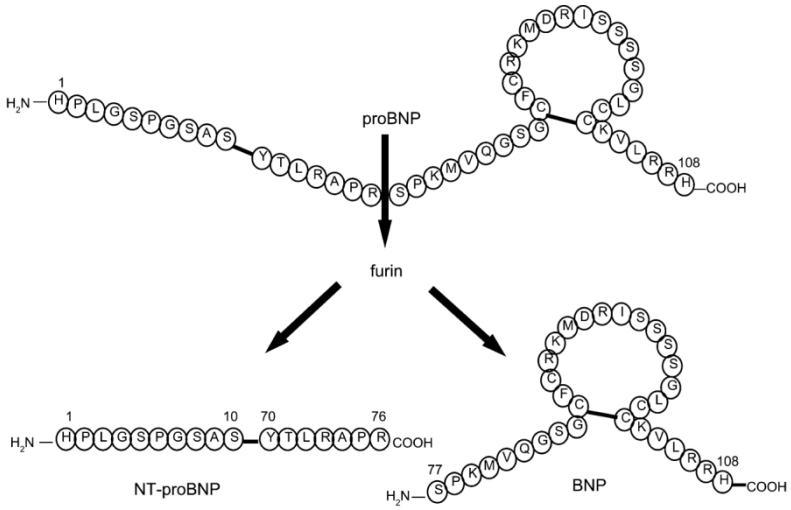


Figure 1. proBNP – enzymatic cleavage in BNP active form and unactive NT-proBNP

4.2 Secretion of NT-proBNP

Cardiac myocites represent the major source for BNP type peptide in the blood stream. A recent discovery highlited the role of fibriblats in the conception of BNP . This finding is still unclear by the actual mechanism pathways. The main stimulum for production and eliberating of ANP și BNP the myocardial wall stress. *in vitro Experiments* indicated that the realase of BNP on paracrine or endocrine way is modulated by specific neurohormones in acute atrial stress. If we speack about atrial stress, then we speack about a higher realese and a proper responde of ANP. This is another argument for attributing a ventricular origin to the the BNP hormone. It is also a clear fact proven that when a pathology regarding ventricular suffering with ischemic events occurs such as myocardial infarction, we have a higher expression for BNP rather than ANP.

PERSONAL RESEARCH PART

PERSONAL STUDY TARGHETS

1. The evaluation of the relationship between enzymatic rates and şi the patients general clinical state who suffered a major traumatic event mostly implying the thoracic wall as a predictive positive outcome
2. Primary survey in the Emergency room of the patients and 24 hours
3. Identify the enzymatic abnormalities and their dynamic changes from the admission in the ED and in the first 12 hours of hospitalisation
4. Identify the imagistic patterns and how they change during the evolution of the patients
5. Imidiate outcome , surviving expectations at 12 h and şi and departure /death
6. Evaluation of the predictive role of the enzymatic, imagistic and epidemiology parameters amongst

MATERIALS AND METHODES

I included in this study a group of 33 patients with severe thorax politrauma due to vehicle accidents, registrated in the Emergency Room of the Constanta Emergency Clinical Hospital. The study was made in 4 years , and I present the following Criteria:

STUDY PROTOCOL

I. Primary survey

II. A. Biological enzymatic determinations

B. Imagistic results at admission and followup 12-24 h

III. Analysis of the results obtained

IV. Creating a data base for all the findings

I.Clinical evaluation of the patients:

- Evaluation of the accident mechanism and the cause of the traumatic event
- Primary survey in the Emergency room
- Monitoring the patient – vital signs, blood pressure, SpO2, heart rate, ECG

II Biological examn:

A. Laboratory findings:

1. ASTRUP arterial punction

2. Venous punction : CBC, Troponin I, CK-MB, NT-proBNP

NT-PRO BNP(reference value of 125 pg/mL)

The biological tests were made in the personal ED with : SYSMEX XS 1000i, for CBC, COBAS INTEGRA 400, COBAS h232, RESPONE BIOMEDICAL for cardiac enzymes.

Imagistic examination::

All of them are made with the specification the the emetgency clinician respecting all the trauma emergency protocols

CLINICAL STUDY INCLUSION CRITERIA

1. Age over 16 years old
2. Diagnostic of severe thoracic trauma in pre-hospital.
3. Existance of medical documents that provide informations about the patients past clinical history with no cardiac pathology , monitorisation, evaluation chart, enzymatic notes and imagistic ones at submission and at 12 h after.
4. Documented data requiring the mechanisms of trauma, general state of the patient

CLINICAL STUDY EXCLUSION CRITERIA

1. Minor patients <16 yrs
2. Patients with no thoracic trauma or minor lesions
3. Patients with no medical history documents or with no possibility of following data
4. Patients with no information about the traumatic events (spoken or documented

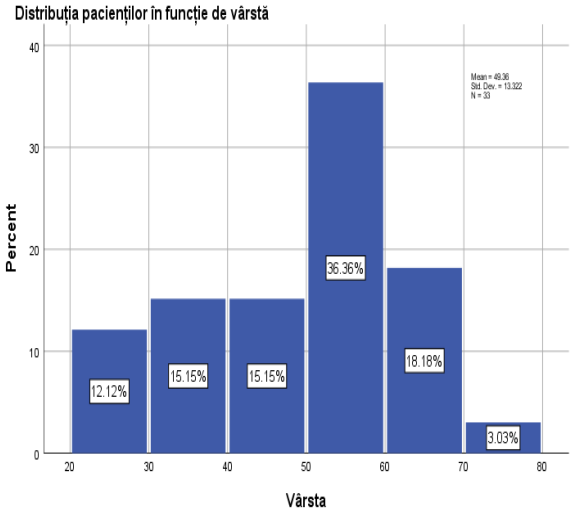
4. RESULTS

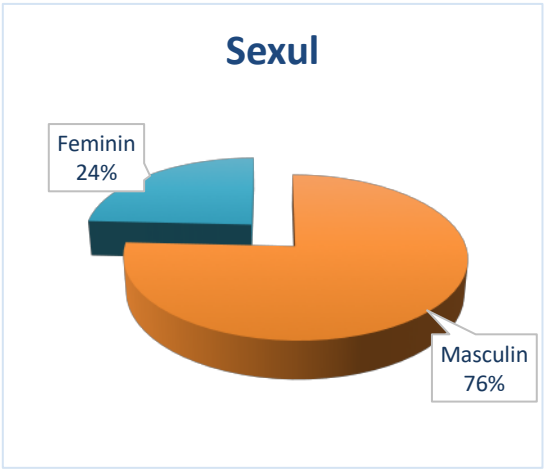
AGE

Over 57% of the patients have 50 years old

SEX

The majority of the patients were male victims summing up a 76% of total .

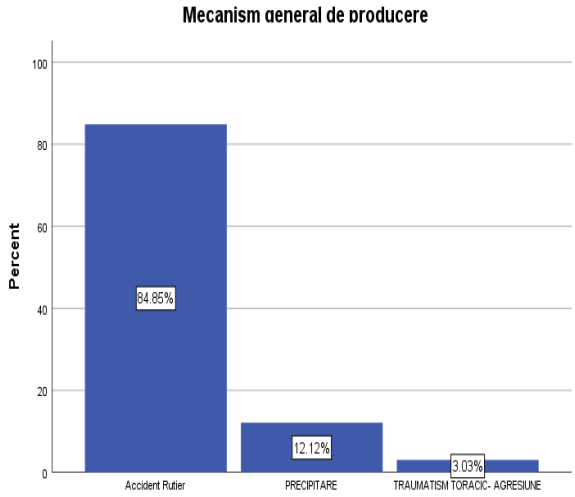


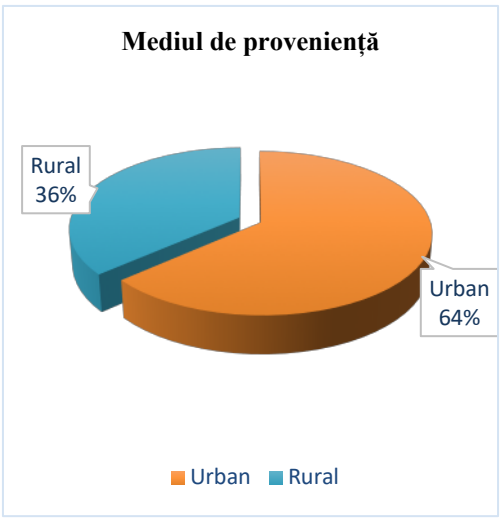


Figures 2,3 Distribution of the patients regarding age and sex

MECHANISM OF THE TRAUMATIC EVENT

Very important for the primary survey and also to evaluate the pissible complications, car crash events representing 85%, followed by traumatic falls and physical aggression, 40% of the patients being drivers ,24,24% right seated patients, 64% of the victims having an urban origin





Figurres 4, 5 traumatic mechanism and origin

A. Clinical evaluation

General status

At the primary survey I noted that 42% of the patients were initially stable, the rest of them having an alterated general response, with clinical instability signs.

Glasgow Coma Scale

36%. Of the patients had a low value of GCS score with deeply implication of the neurological status , GCS 3 was evaluated in 21,21%, of the cases.

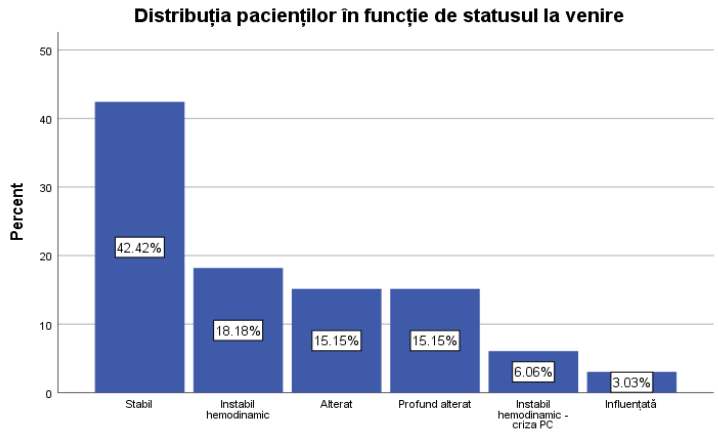


Figure 6. General status at presentation

SpO2 values were 95 – 99%, in a percent of 36,36 of patients , with good breathing response

Orotraheal Intubation

As a result of the critical status of the patients, 36,4% of the victims were intubated to protect the airwaves and to supply proper oxygenation levels.

Systolic blood pressure and Dyastolic blood pressure

33,33% were hypotensive with values of 110 – 129 /90 – 119

Heart rate and arrhythmias

-there were two types of patients mostly with the same prevalence: one group with normal heart rate, another one with bradicaric rhythm 33,33% and a high incidents of tachiarrhythmias with medium frequency 100-115 bpm (30,30%) such as Atrial Fibrilation with fast ventricular response 50% , followed up by severe atrio-ventricular block25%. With ventricular extra beats.

B. BIOLOGICAL FINDINGS

B1.CK-MB at admission , 88% had elevated values with sevrere muscular injury

B2. CK-MB series

Starting with 24U/L as a normal value for this biomarker , only 15% of the patients had normal levels.

B3. Troponin I at admission

Negative in results lower than 0,02 ng/ml(40%),

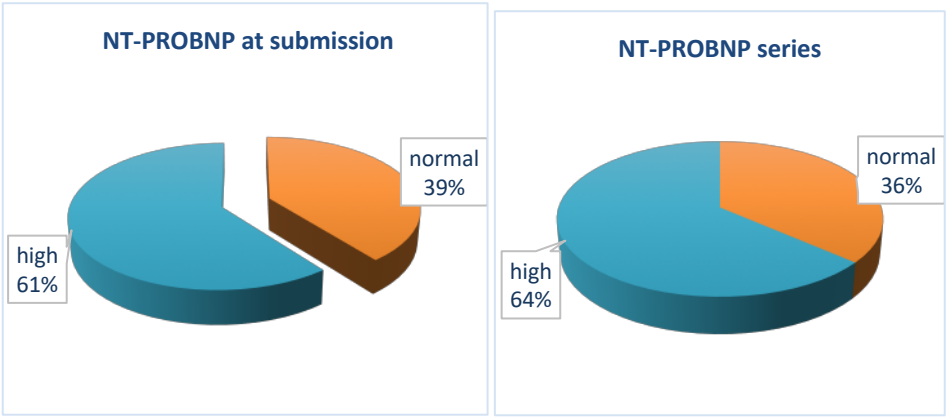
Positive + in results more than 0,02 – 0,059 ng/ml(27%),

B4. Troponin I series

45,45% of the patients had no enzymatic hish rates, representing the exclusion of myiocardial infarction in this cathegory

B5. NT-PROBNP

61% had values at the first prelevation much higher that the normal state, with an evolution in numbers up to 64%, the medium value reported was 462,03U/L and a maxim nuber of 6580 U/L



Figurile 7,8 NT-proBNP values

C. RADIOLOGY RESULTS

56% presented multiple rib fractures, 12% severe haemothorax, 19% associated upper limb fractures and 25% lower limb fractures such ar complete right femour fracture

D. CARDIAC ULTRASOUND

Whithin the echocardiological findings- trans thoracic ultrasound- the most impotant of them are as expected the presence of pericardial effusion with different measured volumes, rupture of valvular cordage and aneurisms. This procedure was performed by the cardiologist doctor on call in the emergency room, after the primary survey practiced by the emergency doctor to evaluate the function of the hear and the cardiac outcome of the patients.

D1.ECHOCARDIOGRAPHY CHECK

The pathology encountered was complex and associated with the initial findings or with the severity of the outcome and then with the interventional procedures. I noticed that at a percent of 6,1 of the cases, the pericardial fluid was still present in the subxifoidian loop mostly at a quantity of 8mm in the right ventricle. I also noticed the positive evolution of the drainage of cardiac tamponade. Still there has been a worrying number of patients in which the cardiac ultrasound confirmed the asistola..

HAEMODINAMIC STATUS

-80% of the patients had an abnormal WBC level at presentation due to hypovolemic shock imparing a percent of 20 norohaemodynamic patients. This fact proves the severity of the impact with a response in internal bleeding or severe acute anemic syndromes.

Leukocitosis due to traumatic shock and sepsis contributed in the complex approach in treatment and management for severe politrauma patients. Up to 42% had values 12,5 – 15 $*10^3/mm^3$. And sever cases with sepsis (9%) , $35*10^3$ $/mm^{3,}$

5. DISCUSION

- The patients who passed the inclusion criteria for the study were mainly male patients (75,8%), older than 50 years (57%), drivers, cars crash victims. (80%),

- At the primary survey in the ED, although the majority of them had stable vital signs(40%), a oercent of 20 had a deeply alterated neurological status with a GCS 3 points who needed mechanical respiratory support (36%).

- Durig the secondary survey we prelevated biological blood tests. The worring results revealed the incidence of hypovolemic shock, leukocytosis, muscular injury and possible acute cardiac traumatic event with NT-proBNP serum levels elevated.

- To confirm the cardiac injury and to masure the cardiac output we performed a cardiac ultrasound in the ED. This imagistic approach showed in a majority of cases the presence of cardiac tamponade and pericardial effusion that were immediately drained. It also confirmed in some situations a NON-STEMI myocardial infarction

- The emergency physician recommended a series of imagistic investigations adapted to the pathological findings and useful to complet the diagnosis.Radiological findings were mainly regarded to rib fractures, haemothorax and limb fractures

- CT scans also associated in 30% of the cases traumatic brain injuries, pulmonary concussions and haemothorax.

- Following the evolution of the patients 30% had a poor outcome, 21% f them with deep alteration of neurological status , NT-proBNP resultls in 24 hours maintaining increased..

- I suspected a connection between the traumatic event and biomarker high rates and a prognostic role of it can be attributed, showing once again the importance of time and management in cardiac trauma.

LONG TERM PERSPECTIVE

Non invasive procedure , no additional costs, with major impact for the politrautized patients outcome and with a result obtained in short time.

6.THESIS ORIGINAL CONTRIBUTION

With this paper I had the aim to prove a predictive role and vital importance in determinating NT-proBNP in Emergency Units in the case of patients with severe traumatic chest lesions.

There are no recent studies to comlet all the researches about this subject and also to find proper correlations between acute ventricular inurty and enzymatic rates.

Introducing in the approach of the politraumatized patients in the current practice of emergency departments the prognostic value of NT-proBNP it would be a real life-saving porcedure in risk stratification and outcome. There are no suplimentary costs added, and the results are obtained in short time up to 5 minute.

Due to the high mortality rates worldwide this enzyme might provide an improvement in the management and surviving rates of traumatic heart injuryes.

7.GENERAL CONCLUSIONS

1. Politraumatic patients and thoracic trauma have an increased mortality rate worldwide sencondary to acute pathology but also to the vital complications.
2. An adequate diagnosis of the primary lesions and an appropiate management of medical resources are essential keys for surviving
3. Post traumatic heart pathology puts in difficulty for many times the physician in order to establish a correct diagnosis
4. NT-proBNP values might have a prognostic role associated with clinical asses and imagistic findings
5. Obtaining the result of the blood tests requires a minim invasive procedure with no suplimentary costs in the ED.
6. Applicable in all Emergency Units and in prehospital
7. The information regarding the value of the biomarkes is given in short time

BIBLIOGRAPHY

1. American Collegeof Surgeons Committeeon Trauma. Advanced Trauma Life (ATLS®), Support Program for Doctors, 7th edn. Chicago, IL: American Collegeof Surgeons, 2004.
2. Bansal MK, Maraj S, Chewaprooug D, Amanullah A: Myocardial contusion injury: redefining the diagnostic algorithm. Emerg Med J 2005; 22: 465.
3. Bhardwaj A, Januzzi JL. Natriuretic peptide-guided management of acutely destabilized heart failure. Rationaleand treatment algorithm. Critical Pathways Cardiol 2009; 8:146–150.
4. Bock JS, Benitez RM: Blunt cardiac injury. Cardiol Clin 2012; 30: 545.
5. Branney SW, MooreEE, Cantrill SV, et al. Ultrasound based key clinical pathway reduces the useof hospital resources for the evaluation of blunt abdominal trauma. J Trauma 1997;42(6): 1086–90.
6. Baker SP, O'Neill B, Haddon W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974; 14: 187–196.
7. Ball C, Williams B, Wyrzykowski A, et al: Acaveat to the performanceof pericardial ultrasound in patients with penetrating cardiac wounds, J Trauma 67:1123-1124, 2009
8. BarbatoE, Rubattu S, Bartunek J, Berni A, Sarno G, Vanderheyden M, Delrue L, Zardi D, Pace B, De Bruyne B, Coluccia R, WijnsW
9. Bastida JL, Aguilar PS, González BD. Theeconomiccosts of trafficaccidents in Spain. J Trauma 2004; 56: 883–889.
10. BouamraO, Wrotchford AS, Hollis S, Vail A, Woodford M, Lecky FE. A new approach tooutcome prediction in trauma: acomparison with the TRISS model. Journal of Trauma 2006; 61:701–710.
11. Boerrigter G, Costello-Boerrigter LC, Burnett JC Jr. Natriuretic peptides in the diagnosis and management of chronic heart failure. Heart Fail Clin 2009; 5:501–514.
12. Chiara O, Cimbanassi S. Organized traumacare: does volume matter and do traumacenters save lives? Curr Opin Crit Care 2003; 9(6):510–14.
13. CRASH-2 Trial Collaborators, Roberts I, Shaku H, et al: The Importanceof early treatment with tranexamicacid in bleeding trauma patients: an exploratory
14. Currie MG, Geller DM, Cole BR et al. Bioactivecardiac substances: potent vasorelaxant activity in mammalian atria. Science 1983; 221:71–73.

15. Cao L, Gardner DG. Natriuretic peptides inhibit DNA synthesis in cardiac fibroblasts. Hypertension 1995;25:227–234.
16. Committee on injury scaling, Association for theAdvancement of Automotive Medicine. TheAbbreviated Injury Scale. 1990 Revision. Update 98. Des Plaines, Illinois: 1990.
17. Cocchi M, Kimlin E, Walsh M, et al. Identification and resuscitation of the trauma patient in shock. Emerg Med Clin N Am 2007; 25(3):623–42.
18. Dan Dermengiu, George C, Valentin G. Medicinã legalã : Note de curs 2011; DOI:10.5682 / 9786065912717
19. Desouza KA, Desouza NA, Pinto RM, et al: Transthoracic echocardiogram is a useful tool in the hemodynamic assessment of patients with chest trauma. Am J Med Sci 2011; 34: 340.
20. Di Bartolomeo S, Sanson G, Michelutto V, Nardi G, Burba I, Francescutti C, Lattuada L, Scian F. The regional study-group on major injury. Epidemiology of major injury in the population of Friuli Venezia Giulia – Italy. Injury, Int J Care Injured 2004; 35: 391–400.
21. Driscoll P, Lecky F. Primary prevention is better than cure. Emergency MedicineAustralasia 2004; 16:265–266.
22. Drewett JG, Garbers DL. The family of guanylyl cyclase receptors and their ligands. Endocr Rev 1994; 15:135–162.
23. Dutton RP, MackenzieCF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma 2002; 52(6):1141–6.
24. de Bold AJ, Borenstein HB, Veress AT et al. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 1981;8:89–94.
25. de Bold AJ. Heart atria granularity effects of changes in water-electrolyte balance. Proc SocExp Biol Med 1979;161:508–511.
26. Del Ry S, Cabiati M, Lionetti V, Emdin M, Recchia FA, Giannessi D. Expression of C-type natriuretic peptideand of its receptor NPR-B in normal and failing heart. Peptides 2008; 29:2208–2215.
27. Demetriades D, Murray J, Sinz B, Myles D, Chan L, Sathyaragiswaran L, Noguchi T, Bongard FS, Cryer GH, Gaspard DJ. Epidemiology of major traumaand trauma deaths in Los Angeles County. J Am Coll Surg 1998; 187: 373–383.
28. Elie MC: Blunt cardiac injury. Mt Sinai J Med 2006; 73: 542.

29. El-Menyar A, Al Thani H, Zarour A, Latifi R: Understanding traumatic blunt cardiac injury. Ann Card Anaesth 2012; 15: 287.
30. Flynn TG, de Bold ML, de Bold AJ. Theaminoacid sequenceof anatrial peptide with potent diureticand natriuretic properties. Biochem Biophys Res Commun 1983; 117:859–865.
31. Guillamondegui OD, Pryor JP, Gracias VH, et al. Pelvic radiography in blunt trauma resuscitation: a diminishing role. J Trauma 2002;53(6):1043–7.
32. Gambaryan S, Wagner C, Smolenski A, et al. Endogenous or overexpressed cGMP-dependent protein kinases inhibit cAMP-dependent renin release from rat isolated perfused kidney, microdissected glomeruli, and isolated juxtaglomerular cells. Proc Natl Acad Sci U S A 1998; 95:9003–9008.
33. Goetze JP, Kastrup J, Pedersen F, Rehfeld JF. Quantification of pro-B-type natriuretic peptideand itspr oducts in human plasma by useof an analysis independent of precursor processing. Clin Chem 2002; 48:1035 –42.
34. Hoffman JR, Wolfson AB, Todd K, et al. Selective cervical spine radiography in blunt trauma: methodology of the National Emergency X-Radiography Utilization Study (NEXUS). Ann Emerg Med 1998;32(4):461–9.
35. Http://responsebio.com/cardiovascular/nt-probnp
36. Http://responsebio.com/cardiovascular/troponin-I
37. http://www.euro.who.int/eprise/main/WHO/InformationSources/Data/2005
38. https://drmjjr.blogspot.com/2012/09/notes-forensic-traumatology.html
39. https://fineartamerica.com/featured/haemopericardium-pr-r-abelanet-cnri.html
40. https://cardioguard.files.wordpress.com/2017/07/comotio-cordis-softball1.jpg
41. Hunt PJ, RichardsAM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA. Immunoreactiveamino-terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. Clin Endocrinol 1997; 47:287 –96.
42. Hunt PJ, Yandle TG, NichollsMG, Richards AM, Espiner EA. Theamino-terminal portion of pro-brain natriuretic peptide (Pro-BNP) circulatesin human plasma. Biochem Biophys Res Commun 1995; 214:1175 –83.
43. Hystad ME, Geiran OR, Attramadal H, Spurkland A, VegeA, Simonsen S, et al. Regional cardiacexpression and concentration of natriuretic peptidesin patients with severechronic heart failure. Acta Physiol Scand 2001; 171:395 –403.
44. Hall C. Essential biochemistry and phisiology of (NT-pto)BNP. TheEur J of Heart Fail 2003; 6:257-260.

45. Harada M, Saito Y, Kuwahara K, OgawaE, Ishikawa M, NakagawaO, et al. Interaction of myocytesand non-myocytes is necessary for mechanical stretch to induceANPyBNP production in cardiocyteculture. J Cardiovasc Pharmacol 1998;31(suppl 1): S357 –359.
46. He JG, Chen YL, Chen BL, Huang YY, Yao FJ, Chen SL, Dong YG. B-type natriuretic peptideattenuates cardiac hypertrophy via TGF-beta1/smad7 pathway in vivoand in vitro. Clin Exp Pharmacol Physiol 2009.
47. Heublein DM, Huntley BK, Boerrigter G, Cataliotti A, Sandberg SM, Redfield MM, Burnett JC, Jr. Immunoreactivity and guanosine 3',5'-cyclic monophosphateactivating actions of various molecular forms of human B-type natriuretic peptide. Hypertension 2007; 49:1114–1119.
48. Hoyt DB, Coimbra R, Potenza B. Management of acute trauma. In Townsend CM, Beauchamp RD, Evers BM, et al. (eds.), Sabiston Textbook of Surgery, 17th edn. Philadelphia, PA: WB Saunders, 2004: pp. 311–44.
49. J. Bayer, R. Lefering, S. Reinhardt, J. Kühle N. P. Südkamp, T. Hammer and Trauma Register DGU. Severity-dependent differences in early management of thoracic trauma in severely injured patients - Analysis based on the Trauma Register DGU.*Scandinavian Journal of Trauma, ResuscitationandEmergency Medicine* 2017;25:10
50. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of theAmerican Collegeof Cardiology Foundation/American Heart Association Task Forceon Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:1977–2016.
51. Kirkpatrick AW, Sirois M, Laupland KB, et al. Hand-held thoracic sonography for detecting post-traumatic pneumothoraces: TheExtended Focused Assessment with Sonography for Trauma (EFAST). J Trauma 2004;57(2):288–95.
52. Kirchhoff C, Stegmaier J, Bogner V, Buhmann S, Mussack T, Kreimeier U, Mutschler W, Biberthaler P: Intrathecal and systemicconcentration of NT-proBNP in patients with severe traumatic brain injury. J Neurotrauma 2006, 23:943-949.

53. Kia M, Cooley A, Rimmer G, MacDonald T, Barber K, Manion P, Shapiro B, Socey J, Iddings D: Theefficacy of B-type natriuretic peptide for early identification of blood loss in traumatic injury.Am J Surg 2006, 191:353-357.
54. Kjetil Søreide, Andreas J. Krüger, Anne Line Vårdal, Christian LyckeEllingsen, Eldar Søreide, Hans Morten Lossius. Epidemiology and Contemporary Patterns of Trauma Deaths: Changing Place, Similar Pace, Older Face. *World J Surg* 2007;31:2092.
55. Knudtson JL, Dort JM, Helmer SD, et al. Surgeon performed ultrasound for pneumothorax in the trauma suite. J Trauma 2004; 56(3):527–30.
56. Krug EG, Sharma GK, Lozano R. The Global Burden of Injuries. Am J Public Health 2000; 90: 523–526.
57. Kuhn M. Molecular physiology of natriuretic peptide signaling. Basic Res Cardiol 2004; 99:76–82.
58. Kursch B. Electron microscopy of theatrium of the heart. Exp Med Surg 1956; 13:99-111.
59. Kaleghi M, Al-Omari MA, Kondragunta V, Morgenthaler NG, Struck J, Bergmann A, Mosley TH, Kuoo IJ. Relation of plasma midregional natriuretic peptide to target organ damage in adults with systemic hypertension. Am J Cardiol 2009; 103: 1255–1260.
60. Kangawa K, Matsuo H. Purification and completeaminoacidsequenceof alpha-human atrial natriuretic polypeptide (alphathehANP). Biochem Biophys Res Commun 1984;118:131–139.
61. Karmali S, Laupland K, Harrop AR, Findlay C, Kirkpatrick AW, Winston B, Kortbeek J, Crowshoe L, Hameed M. Epidemiology of severe traumaamong status aboriginal Canadians: a population-based study. CMAJ 2005; 172: 1007–1011.
62. Lateef Wani M, Ahangar AG, Wani SN, Irshad I, Ul-Hassan N: Penetrating cardiac injury: a review. Trauma Mon 2012; 17: 230.
63. Li P, Wang D, Lucas J, et al. Atrial natriuretic peptide inhibits transforming growth factor beta-induced Smad signaling and myofibroblast transformation in mousecardiac fibroblasts. Circ Res 2008; 102:185–192.
64. Livingston DH, Lavery RF, Passannante MR, et al. Admission or observation is not necessary after a negativeabdominal computed tomographic scan in patients with suspected blunt abdominal trauma: results of a prospective, multi-institutional trial. J Trauma 1998; 44(2):273–80.

65. Liang F, O'Rear J, Schellenberger U, et al. Evidence for functional heterogeneity of circulating B-type natriuretic peptide. J Am Coll Cardiol 2007; 49:1071–1078.
66. Liener UC, Rapp U, Lampl L, Helm M, Richter G, Gaus M, Wildner M , Kinzl L, Gebbhard F. Incidenceof severe injuries. Results of a population – based analysis. Unfallchirurg 2004; 107: 483–490.
67. Lyons RA, Jones SJ, Deacon T, Heaven M. Socioeconomic variation in injury in children and older people: a population based study. Inj Prev 2003; 9: 33–37.
68. Labovitz AJ, Noble VE, Bierig M, et al: Focused cardiac ultrasound in theemergent setting: aconsensus statement of theAmerican Society of Echocardiography and American Collegeof Emergency Physicians, J Am SocEchocardiogr 23(12):1225-1230, 2010.
69. Lassus J, Gayat E, Mueller C, Peacock WF, Spinar J, Harjola V-P, van Kimmenade R, Pathak A, Mueller T, Di Somma S, Metra M, Pascual-Figal D, Laribi S, Logeart D, Nouira S, Sato N, Potocki M, Parenica J, Collet C, Cohen-Solal A, Januzzi JL Jr, MebazaA for the Great-Network. Incremental valueof biomarkers toclinical variables for mortality prediction in acutely decompensated heart failure: The Multinational Observational Cohorton on Acute Heart Failure (MOCA) study. Int J Cardiol 2013; 168:2186–2194.
70. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, Watson C, O'Hanlon R, Bermingham M, PatleA, Badabhagni MR, Murtagh G, Voon V, Tilson L, Barry M, McDonald L, Maurer B, McDonald K. Natriuretic peptide-based screening and collaborativecare for heart failure: the STOP-HF randomized trial. JAMA 2013; 310:66–74.
71. LegomeE, Shockley LW. TraumaAComprehensiveEmergency MedicineApproach. Cambridge University Press 2011.
72. LeeCY, Burnett JC Jr. Natriuretic peptides and therapeuticapplications. Heart Fail Rev 2007; 12:131–142.
73. Molina EJ, Gaughan JP, Kulp H, et al: Outcomes after emergency department thoracotomy for penetrating cardiac injuries: a new perspective. Interact Cardiovasc Thorac Surg 2008; 7: 845.
74. Mrochuk M, Odochartaigh D, Chang E: Rural trauma patients cannot wait: tranexamicacid administration by helicopter emergency medical services. AirMed J 2015; 34: 37.

75. Murray CL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020. Lancet 1997; 349: 1498–1504.
76. Murakami S, Nagaya N, Itoh T, et al. C-type natriuretic peptideattenuates bleomycin-induced pulmonary fibrosis in mice. Am J Physiol Lung Cell Mol Physiol 2004; 287:L1172–L1177.
77. Mair J. Clinical significanceof pro-B-type natriuretic peptide glycosylation and processing. Clin Chem 2009; 55:394–397.
78. Maier B, Lefering R, Lehnert M, Laurer HL, Steudel WI, Neugebauer EA, Marzi I: Early versus lateonset of multipleorgan failureis associated with differing patterns of plasmacytokinebiomarker expression and outcomeafter severe trauma.*Shock* 2007, 28:668-674.
79. Mandavia DP, Joseph A. Bedsideechocardiography in chest trauma. Emerg Med Clin North Am 2004; 22(3):601–19.
80. Mantymaa P, VuolteenahoO, Marttila M, Ruskoaho H. Atrial stretch induces rapid increase in brain natriuretic peptide but not in atrial natriuretic peptide geneexpression in vitro. Endocrinology 1993; 133:1470 –3.
81. Mathews L, Singh RK: Cardiacoutput monitoring. Ann CardAnaesth 2008, 11:56-68.
82. Mohr AM, Holcomb JB, Dutton RP, et al. Recombinant activated factor VIIaand hemostasis in critical care: a focus on trauma. Crit Care 2005; 9(Suppl. 5):S37–42.
83. Nadler EP, Potoka DA, Shultz BL, et al. The high morbidity associated with handlebar injuries in children. J Trauma 2005; 58(6):1171–4.
84. Nakao K, Kanagawa K. The natriuretic peptide family 1st Edition. TokyoL Kodansha Scientific 1995.
85. Nemer M, Lavigne JP, Drouin J, Thibault G, Gannon M, Antakly T. Expression of atrial natriuretic factor gene in heart ventricular tissue. Peptides 1986; 7:1147–1152.
86. Pauze DR, Pauze DK: Emergency management of blunt chest trauma in children: an evidence-based approach. Pediatr Emerg Med Pract 2013; 10:1.
87. Philip L, Dimitrios K:Critical Care Ultrasound, Elsevier Saunders,ISBN: 978-1-4557-5357-4, 2015
88. Pape H-C, Zelle B, Lohse R, Hildebrand F, Krettek C, Panzica M, Duhme V, Sittaro NA. Evaluation and outcomeof patients after polytrauma – Can patients be recruited for long- term follow up? Injury 2006;37(12):1197–1203.
89. Pasquier M, SierroC, Yersin B, et al: Traumatic mitral valve injury after blunt chest trauma: acase report and review of the literature. J Trauma 2010; 68: 243.

90. Pemberton CJ, Johnson ML, Yandle TG, Espiner EA. Deconvolution analysis of cardiac natriuretic peptides during acute volumeoverload. Hypertension 2000; 36:355 –9.
91. Qi W, Kjekshus J, Hall C. Differential responses of plasmaatrial and brain natriuretic peptidestoacutealteration in atrial pressure in pigs. Scand J Clin Lab Invest 2000; 60:55 –63.
92. Reddy D, Muckart DJ: Holes in the heart: an atlas of intracardiac injuries following penetrating trauma. Interact Cardiovasc Thorac Surg 2014; 19: 56.
93. Rootman DB, Mustard R, Kalia V, et al. Increased incidence of complications in trauma patients cointoxicated with alcohol and other drugs. J Trauma 2007;62(3):755–8.
94. Rubattu S, Sciarretta S, MorrielloA, Calvieri C, Battistoni A, Volpe M.NPR-C: acomponent of the natriuretic peptide family with implications in human diseases. J Mol Med 2010; 88:889–897.
95. Rubattu S, Sciarretta S, Valenti V, Stanzione R, Volpe M. Natriuretic peptides: an updateon bioactivity, potential therapeutic useand implication in cardiovascular diseases. Am J Hypertens 2008; 21:733–741.
96. RestrepoCS, Lemos DF, Lemos JA, et al: Imagingfindings in cardiac tamponade with emphasison CT, Radiographics 27:1595-1610, 2007
97. Roberts I, Shakur H, Ker K, Coats T, CRASH-2 Trial Collaborators: Antifibrinolytic drugs for acute traumatic injury (review). Cochrane Database Syst Rev 2011; 1:CD004896.
98. Rosen C, LegomeEL, Wolfe RE. Blunt abdominal trauma. In Adams J (ed.), Emergency Medicine. Philadelphia, PA: WB Saunders, 2008: pp. 827–40.
99. Schultz JM, Trunkey DD: Blunt cardiac injury. Crit Care Clin 2004; 20: 57.
100. Shamsi F, Tai JM, Bokhari S: Coronary artery dissection after blunt chest trauma. BMJ 2014; Case Rep September 22.
101. Skinner DL, Laing GL, Rodseth RN, Ryan L, Hardcastle TC, Muckart DJ: Blunt cardiac injury in critically ill trauma patients: a singlecentreexperience. Injury 2014; 46: 66.
102. Smith MW, Espiner EA, Yandle TG, Charles CJ, Richards AM. Delayed metabolism of human brain natriuretic peptide reflects resistance to neutral endopeptidase. J Endocrinol 2000; 167:239 –46.

103. Spencer RJ, Sugumar H, Jones E, Farouque O: Commotio cordis: a case of ventricular fibrillation caused by a cricket ball strike to the chest. Lancet 2014; 383: 1358.

104. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriureticpeptide in porcine brain. Nature 1988;332:78–81.

105. Sudoh T, Minamino N, Kangawa K, Matsuo H. C-type natriureticpeptide (CNP): a new member of natriuretic peptide family identified in porcine brain. Biochem Biophys Res Commun1990;168:863–870.

106. Sybrandy KC, Cramer MJ, Burgersdijk C: Diagnosing cardiaccontusion: old wisdom and new insights. Heart 2003; 89: 485.

107. Sabrane K, Kruse MN, Fabritz L, et al. Vascular endothelium is critically involved in the hypotensiveand hypovolemicactions of atrial natriuretic peptide. J Clin Invest 2005; 115:1666–1674.

108. Santaniello JM, Esposito TJ, Luchette FA, et al. Mechanism of injury does not predict acuity or level of service need: field triagecriteria revisited. Surgery 2003; 134(4):698–703.

109. Savarese G, Trimarco B, Dellegrottaglie S, Prastaro M, Gambardella F, Rengo G, Leosco D, Perrone-Filardi P. Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. PLoS ONE 2013; 8: e58287.

110. Sawada Y, Suda M, Yokoyama H, et al. Stretch-induced hypertrophic growth of cardiocytes and processing of brain-type natriuretic peptidearecontrolled by proprotein-processing endoprotease furin. J Biol Chem 1997; 272:20545–20554.

111. Seidman CE, Bloch KD, Zisfein J, et al. Molecular studies of theatrial natriuretic factor gene. Hypertension 1985; 7:I31–I34.

112. Semenov AG, Postnikov AB, Tamm NN, et al. Processing of pro-brain natriuretic peptide is suppressed by O-glycosylation in the region close to thecleavage site. Clin Chem 2009; 55:489–498.

113. Seronde MF, Gayat E, Logeart D, Lassus J, Laribi S, Boukef R, Sibellas F, Launay JM, Manivet P, Sadoune M, Nouira S, Cohen Solal A, MebazaaA. Great Network. Comparison of the diagnosticand prognostic values of B-typeand atrial-type natriuretic peptides in acute heart failure. Intern J Cardiol 2013; 168:3404–3411.

114. Schmidt GA, Koenig S, Mayo PH: Shock: ultrasound to guide diagnosis and therapy, Chest, 142:1042-1048, 2012.

115. Scotland RS, Cohen M, Foster P, Lovell M, Mathur A, AhluwaliaA, Hobbs AJ. C-type natriuretic peptide inhibits leukocyte recruitment and platelet-leukocyte interactions via suppression of P-selectin expression. Proc Natl Acad Sci USA 2005; 102:14452–14457.

116. Talving P, Demetriades D: Cardiac trauma during teenage years. Pediatr Clin North Am 2014; 61: 111.

117. Tintinalli KE. Stapczynski JS, MaOJ, Yealy DM, Mecker HD, Cline DM. Tintinalli's Emergency MedicineAComprehensive Study Guide 8thEdition. American Collegeof Emergency Physicians, McGraw Hill Education 2011.

118. Tsuneyoshi H, Nishina T, Nomoto T, et al. Atrial natriuretic peptide helps prevent late remodeling after left ventricular aneurysm repair. Circulation 2004; 110:II174–179.

119. Tamura N, Ogawa Y, Chusho H, et al. Cardiac fibrosis in mice lacking brain natriuretic peptide. Proc Natl Acad Sci USA 2000; 97:4239 –44.

120. van Veldhuisen DJ, Linssen GC, Jaarsma T, van Gilst WH, Hoes AW, Tijssen JG, Paulus WJ, Voors AA, Hillege HL. B-type natriuretic peptideand prognosis in heart failure patients with preserved and reduced ejection fraction. J Am Coll Cardiol 2013; 61:1498–1506.

121. Volpe M, Francia P, Tocci G, Rubattu S, Cangianiello S, Rao MAE, Trimarco B, Condorelli M. Prediction of long-term survival in chronic heart failure by multiple biomarker assessment: A 15-year prospective follow-up study. Clin Cardiol 2010; 33:700–707.

122. Volpe M, Rubattu S, Burnett Jr J. Natriuretic peptides in cardiovascular diseases: current useand perspectives. Eur Heart J 2014; 35:419-425.

123. Wu C, Wu F, Pan J, Morser J, Wu Q. Furin-mediated processing of Pro-C-type natriuretic peptide. J Biol Chem 2003; 278:25847–25852.

124. www.tarn.ac.uk

125. Yan W, Wu F, Morser J, Wu Q. Corin, a transmembranecardiac serine protease, acts as a pro-atrial natriuretic peptide-converting enzyme. Proc Natl Acad Sci U S A 2000; 97:8525–8529.