

Research Article

Incidence, Associated Clinical Factors and Outcome of Hypertensive Crises in Critically Ill Patients: A Prospective Survey

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Abstract

Background: Hypertensive crises (HCs) are common among critically ill patients. However, little is known of their epidemiology, particularly actual rate and outcome of affected patients. Primary end-point of the study was to assess incidence of and clinical factors associated with HCs in a cohort of patients admitted to a general ICU. Secondary end-point was to assess the impact of HC on patients' outcome.

Methods: All patients consecutively admitted to a general ICU over a 13 months period were included in the study. Incidence of HCs was assessed and associated clinical factors were determined using univariate and multivariate analysis. Length-of-stay and ICU- and in-hospital mortality were evaluated.

Results: Incidence of HCs was 15.4%. Factors independently associated with HCs were: ICU-admission for acute medical conditions, cigarette smoking, cancer, coronary artery disease, chronic atrial fibrillation (p<0.05). ICU length-of-stay and ICU-/ in-hospital mortality rate were higher among patients with HCs (p<0.05).

Conclusion: HCs are common in critically ill patients, even if previously normotensive, and are associated with a worse outcome. Associated clinical factors include acute medical conditions leading to ICU admission, cigarette smoking, cancer, coronary artery disease and chronic atrial fibrillation.

Keywords: Hypertensive crisis; Epidemiology; Risk factors; Mortality; Critical care

Abbreviations: AH: Arterial Hypertension; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HC: Hypertensive Crisis; CAD: Coronary Aartery Disease; CAF: Chronic Atrial Fibrillation

Introduction

Arterial hypertension (AH), defined as Systolic arterial Blood Pressure (SBP) > 140 mmHg and/or Diastolic Blood Pressure (DBP) > 90 mmHg [1] is common, affecting 26% of the world adult population, i.e. about one billion people [2]. Hypertensive crisis (HCs) is defined as a rapid increase in arterial pressure up to above a SBP of 180 mmHg or above, and/or a DBP of 120 mmHg or above i.e., severe acute hypertension [1] and it can be further defined as urgencies or emergencies. Hypertensive urgencies are rapid rises in arterial blood pressure without evidence of worsening organ dysfunction, while during hypertensive emergencies acute target organ damage is evident, affecting mostly the cardiovascular system, the brain and the kidneys [3]. In surgical patients, perioperative acute severe hypertension can be responsible for major cardiovascular events or bleeding from vascular sutures [4]. Moreover, hypertensive crises may contribute to the acute inflammatory response associated to with surgical stress and to the consequent worse outcome [5]. Despite these considerations, little is still known about actual epidemiology of hypertensive crisis among critically ill patients.

The aim of the present study is to assess incidence, associated clinical factors and outcome of hypertensive crisis in a cohort of mixed medical-surgical critically ill patients.

Materials and Methods

Study protocol has been approved by the local Ethical Board. All patients consecutively admitted to a mixed medical-surgical ICU at the University of Florence (Italy) during a 13 months period (1/1/2008-31/1/2009) were considered eligible and prospectively followed. Medical patients were defined as those admitted for acute clinical conditions which did not require surgical treatment 24 hrs before ICU

admission. Trauma patients who did not require surgery were included among medical patients. Surgical patients were those admitted for postoperative monitoring and intensive treatment after elective surgery (planned or unplanned admission) and those admitted after emergency surgery. Exclusion criteria were considered: moribund patients, patients aged < 18 yrs and readmission to the ICU.

Hypertensive crises were diagnosed following the criteria of Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, as arterial blood pressure acutely rising above 180 mmHg (SBP) and/or 120 mmHg (DBP) [1]. Accordingly, "acute severe hypertension" was an alternative definition for this condition [1]. Following these criteria, patients who had one or more hypertensive crisis during their ICU stay were included in the Hypertensive Crisis (HC) group. Patients who were normotensive were included in the control group; patients who were hypertensive prior ICU admission but whose arterial blood pressure was normal during the ICU stay, were considered as controls. Patients whose acute hypertension was directly related to airway manipulation or uncontrolled pain were dropped from HC to control group.

Differences between acutely hypertensive (HC group) and normotensive patients (control group) were evaluated regarding age, gender, ICU admission diagnosis and SAPS II score, as well as the presence of other clinical factors, according to patients' past medical history and medical examination. Differences were evaluated with

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Wilcoxon and t-Student statistical tests (continuous data) and Chisquare test (discrete data). The association between each clinical condition and HCs was evaluated using univariate analysis and Odds ratio (OR) for each factor was calculated. Furthermore, multivariate analysis was used to assess which factors were independently associated to HCs.

To assess the outcome of patients with severe acute hypertension, differences regarding ICU-length of stay and ICU-/in-hospital mortality were evaluated across the two groups of patients using the t-Student and Chi-square tests.

All the statistical methods have been extensively reviewed by a senior statistician and all results are presented as p values, odds ratio and 95% confidence interval (95% CI). A "p" value < 0.05 was considered statistically significant.

Data were analyzed using the STATA 9.1 software (STATA corp., 4905, Lakeway Drive College Station, 77845, Texas, US).

Results

A total of 409 patients were included in the study. Diagnoses at the admission are shown in (Table 1). Of a total of 409 patients, the incidence of HCs was 15.4% (63/409). A total of 111 hypertensive crises were registered in the HC group, i.e. some patients had more than one crisis during their ICU stay. Differences across groups are summarized in (Table 2). Factors associated to HCs were age (median age 72.9 versus 68.9 years, p=0.02), acute medical conditions leading to ICU admission (36.5% versus 24.6, p=0.001), cigarette smoking (17.5% versus 0.29 %, p=0.001), cancer (52.4% versus 37%, p=0.021), vasculopathy (39.7% versus 27.7%, p=0.044), CAD (coronary artery disease) (15.9% versus 6.7%, p=0.049) and CAF (chronic atrial fibrillation) (19% versus 10.4%, p=0.049); see (Table 2).

At univariate analysis, conditions strongly associated to HCs were cigarette smoking (OR 12.4; 95% CI 3.6 to 42.7; p=0.001), cancer (OR 1.9; 95% CI 1.1 to 3.2; p=0.023), vasculopathy (OR 1.8; 95% CI 1.00 to 3.1; p=0.046), coronary artery disease (OR 2.2; 95% CI 1 to 5.1; p=0.049) and atrial fibrillation (OR 2; 95% CI 1 to 4.1; p=0.049). Cigarette smoking was the strongest among them see (Table 3).

At the multivariate analysis, cigarette smoking (OR 13.6; 95% CI 3.8 to 48.7; p=0.001), cancer (OR 1.9; 95% CI 1.1 to 3.4; p=0.026), coronary artery disease (OR 2.4; 95% CI 1 to 5.9; p=0.044) and atrial fibrillation (OR 2.1; 95% CI 1 to 4.5; p=0.049) were all independently associated to HCs (Table 4).

Patients with HCs tended to have longer ICU length of stay (9 versus 3.9 days, p<0.0001) and higher ICU (25.4% versus 13.6%, p=0.037) and inhospital mortality rates (31.7% versus 19.4%, p=0.027); (Table 5)

Discussion

A recent update of the American Heart Association on stroke and heart disease statistics reports that 26% of the all world population is affected by arterial hypertension (AH). This proportion roughly corresponds to one billion people [6]. Furthermore, 1% of all hypertensive patients will face one or more hypertensive crises [6]. Hypertensive crises are defined as acute rises in arterial blood pressure acutely (i.e., severe acute hypertension). During hypertensive crises, ICU admission may be required for aggressive treatment and organ failure management. Actually, severe acute hypertension account for 0.5%-19.6% of all hospital and ICU admissions [6,7,8]. However, little is known about epidemiology of severe acute hypertension in patients already admitted to ICUs.

Actually, due to the high prevalence of AH in the general population, it can be expected that incidence of HCs in ICU patients should be high. In our study we considered 409 patients admitted to a mixed ICU either for acute medical or surgical conditions and none was admitted for acute severe hypertension management. Prevalence of AH in this cohort was 51.3%, while incidence of hypertensive crises was 15.4%. According to JNC criteria [1], 63/409 patients suffered a total of 111 hypertensive crises (HC group), i.e. some patients had more than one crisis. The analysis of demographic, behavioral and clinical data of patients showed that some factors were associated to HCs. Particularly, HCs were associated to older age, cigarette smoking, medical conditions leading to ICU-admission, cancer , vasculopathy, coronary artery disease (CAD) and chronic atrial fibrillation (CAF).

Multivariate analysis showed that cigarette smoking, medical admission to ICU, cancer, coronary artery disease (CAD) and chronic atrial fibrillation (CAF) were independently associated to HCs. These results are not surprising in light of the literature on pathophysiology of hypertension.

Patients who suffered acute severe hypertension were older than those who were normotensive (Table 2). Age has been already found as a risk factor both for AH and HCs. In a retrospective study on 452 patients with hypertensive crisis, Martin and colleagues found that hypertensive emergencies were more frequent in older patients [7]. Age can be related to progressive arterial wall thickening with reduced vascular compliance [9], renal function impairment and hyperactivity of renin-angiotensin-

Elective surgery-planned ICU admission	47.4%
Gastro Intestinal (GI) oncologic	28%
GI not-oncologic	12.6%
Lung resective surgery	9.7%
ear nose throat (ENT) surgery	7.2%
Abdominal vascular surgery	6.3%
Breast surgery	5.8%
Abdominal wall reconstruction	5.8%
Pancreatic surgery	5.3%
Urologic surgery	4.3%
Endocrinological surgery	3.9%
Cholecystectomy	2.9%
Hepato-biliary oncologic surgery	2.4%
Obstetric /Gynecological (Ob/Gyn) surgery	2.4%
Skin cancer surgery	1.9%
Non trauma related splenectomy	1.5%
Elective surgery-unplanned ICU admission	4.2%
Respiratory complications	50%
Cardiovascular complications	33.3%
Surgical complications	11.1%
Post-operative sepsis	5.6%
Surgical emergency	18.6%
Intestinal perforation	33.3%
Bowel obstruction	13.3%
Life threatening surgical complication	8%
Acute cholecystitis/cholangitis	8%
Trauma surgery	7.9%
Subarachnoid hemorrhage	6.7%
Acute limb ischemia	6.7%
Acute intestinal ischemia	4%
Acute Ob/Gyn bleeding	4%
Post-traumatic splenectomy	2.7%
Post-surgical neck hematoma drainage	2.7%
Acute pancreatitis necrosectomy	2.7%
Medical	29.8%
Community acquired pneumonia	34.9%
COPD exacerbation	17.4%
Trauma (not surgery)	9.2%
Urinary sepsis	7.3%
Acute heart failure/cardiogenic shock	6.4%
Acute liver failure	4.6%
Hemorrhagic/ischemic stroke	4.6%
Acute myeloid leukemia	3.7%
Acute renal failure	2.7%
Pre-eclampisa/Eclampsia	2.8%
Soft tissue infection	2.8%
Acute pancreatitis	1.8%
GI bleeding (not surgical)	0.9%
Bacterial meningitis	0.9%

 Table 1: Diagnosis on admission in the ICU

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Associated factors	stors Definition		HC (n° 63)	Controls (n° 346)	p
Age (median ± SD)			72.9 ± 13.17	68.9 ± 14.8	0.02
Gender Male Female		60.9% 39.1%	60.3% 39.7%	61% 39%	0.70
Admission diagnosis					
	Elective surgery-planned ICU admission Elective surgery-unplanned ICU admission Surgical emergency Medical	47.4% 4.1% 18.6% 29.8%	33.3% 7.9% 22.2% 36.5%	53.8% 3.7% 17.9% 24.6%	0.001
SAPS II score (median ± SD)			32 ± 16.4	36.4 ± 14.9	0.05
Cigarette smoking	> 40 packs year	0.03%	17.5%	0.3%	0.001
Cancer	Neoplastic lesion, with or without metastasis, treated or untreated	39.4%	52.4%	37%	0.021
Vasculopathy	Claudicatio intermittens, arterial bypass, vascular gan- grene, arterial insufficiency, untreated chest or abdominal aortic aneurysm	29.1%	39.7%	27.7%	0.044
Coronary artery disease	Stress test or pharmacological inducible chest pain, history of Acute Myocardial Infarction/angina	8%	15.9%	6.6%	0.049
Chronic atrial fibrillation	Chronic Atrial Fibrillation	11.7%	19%	10.4%	0.050
Hypertension	SBP>140 and/or DBP>90	51.3%	66.7%	48.5%	0.068
PTCA/CABG		5.3%	6.3%	2.3%	0.081
Chronic Renal Failure	Creatinine clearance less than 90 ml/min/m ²	8.8%	11.1%	8.4%	0.095
Chronic liver failure	Hepatitis for more than three months, with or without pres- ence of cirrhosis or its complications	6.6%	7.9%	6.4%	0.23
OSAS (Obstructive Sleep Apnea Syndrome)		0.7%	1.6%	0.6%	0.38
DM (Diabetes Mellitus)	ADO or insulin therapy or diabetes-related complications	23.2%	30.2%	22%	0.48
Myocardial infarction		14.1%	9.5%	15%	0.44
Stroke/TIA		3%	8%	2%	0.49
Heart Failure	Progressive dyspnea, according to NYHA classes	13.4%	7.9%	14.4%	0.83
COPD	Progressive dyspnea, with or without specific therapy, with or without home oxygen therapy, with hypoxemia and/or chronic hypercapnia	40%	38.1%	40.5%	0.94

 Table 2: Distribution of clinical and behavioral factors in patients with Hypertensive Crises (HC) and controls.

Associated Factor	% HC/% Controls	OR	95% CI	Р
Admission Diagnosis		0.7	0.6 – 1	0.046
Cigarette smoking	17.5/0.3	12.4	3.6 - 42.7	0.001
Cancer	52.4/37	1.9	1.1 - 3.2	0.023
Vasculopathy	39.7/27.7	1.8	1 -3.1	0.046
Coronary artery disease	15.9/6.6	2.2	1 -5.1	0.049
Chronic atrial fibrillation	19/10.4	2	1- 4.1	0.049
Hypertension	66.7/48.5	1.7	1 - 2.9	0.070
PTCA/CABG	6.3/2.3	2.9	0.8 - 9.8	0.094
Chronic Renal Failure	11.1/8.4	2	0.9 - 4.4	0.100
Chronic liver failure	7.9/6.4	0.4	0.1 - 1.8	0.247
OSAS	1.6/0.6	2.8	0.2 - 31.1	0.408
DM	30.2/22	1.3	0.7 - 2.3	0.443
Myocardial infarction	9.5/15	0.7	0.3 - 1.7	0.449
Stroke/TIA	7.9/2	0.5	0.1 - 3.9	0.500
Heart Failure	7.9/14.4	1.1	0.5 - 2.3	0.832
COPD	38.1/40.5	1	0.6 -1.7	0.942

Table 3: Univariate Analysis of factors associated with Hypertensive Crisis.

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Associated Factor	% HC/% Controls	OR	95 % CI	Р
Admission Diagnosis		0.73	0.54 to 1.00	0.049
Cigarette smoking	17.46/0.29	13.57	3.78 to 48.71	0.001
Cancer	52.38/36.99	1.92	1.08 to 3.43	0.026
Coronary artery disease	15.87/6.65	2.45	1.02 to 5.91	0.044
Chronic atrial fibrillation	19.04/10.40	2.11	0.99 to 4.50	0.049

Table 4: Multivariate analysis of factors associated to Hypertensive Crisis.

Outcome indexes	All patients	HC (%)	Controls (%)	Р
ICU length of stay (days)		9 ± 12.43	3.87 ± 6.45	<0.0001
Mortality in ICU	15.4%	25.39%	13.58%	0.037
Mortality in Hospital	21.27%	31.74%	19.36%	0.027

Table 5: Clinical outcomes of patients with and without Hypertensive Crisis.

aldosterone system [10], enhanced release of sympathicomimetic mediators [11] and worsening insulin resistance [12]. Increasing age is also associated to a pro-inflammatory status which may contribute to endothelial dysfunction and to a microvascular imbalance towards a vasoconstrictive tone. All these conditions potentially cause or maintain AH and contribute to trigger or maintain hypertensive crises [5]. However, multivariate analysis failed to show age as an independent factor for acute severe hypertension. This is because influence of age on acute hypertension can be due to concomitant co-morbidities (e.g. chronic atrial fibrillation or coronary artery disease) rather than age "per se".

Previous cigarette smoking (more than 40 packs/year) was strongly associated to severe acute hypertension in our ICU population (Table 4). Martin and colleagues found that cigarette smoking was a risk factor for HC in 23.6% of patients included in their study [7]. Smoking-linked etiologic factors for hypertensive crisis may be related to a chronic mild inflammatory status with a shift towards an endothelin-mediated vasoconstrictive tone [7] and an increased nitric oxide degradation [13], with chronically elevated peripheral resistances. In larger blood vessels, smoking causes intimal hyperplasia [14]. Moreover, cigarette smoking exerts a direct vasoconstrictive effect, which is particularly evident on small vessels, including coronary arteries [15].

A very interesting association was found between cancer diagnosis and HCs in our patients' population (Table 4). Escalante and colleagues found that arterial hypertension was the commonest pathological condition leading to acute treatment in 143 cancer patients admitted to the emergency department [16]. Different factors may contribute. Severe acute arterial hypertension can be directly related to release of mediators by neoplastic cells, as in the pheocromocytoma, adrenal gland neoplasms or other endocrine tumors [17]. However, none of the patients included in our study were diagnosed as such. Intriguingly, the pro-inflammatory state associated to cancer, with an increase in circulating levels of IL-1, 6 and TNF-alfa, can play a role in increasing peripheral vascular resistance, thus contributing to hypertensive states [18]. Experimental data show that proinflammatory cytokines can inhibit endothelial constitutive Nitric Oxide-synthase activity, and unopposed endothelin-mediated vasospasm may ensue. This could trigger or maintain high blood pressure [19]. Chronic mild vasospasm may also contribute to endothelial hypoxia and dysfunction, with progressive loss of autoregulatory mechanisms, which predispose patients to organ damage associated to brisk alterations in blood pressure [20]. In cancer patients, cigarette smoking may contribute to a chronic pro-inflammatory state (see above).

Indeed, pathophysiological and epidemiological links between AH and vasculopathy have been well established [21]; however, multivariate

analysis showed that in our study population vasculopathy was not independently associated to HCs. In the big, multicenter "STAT" registry study on acute hypertension treatment the prevalence of vasculopathy or CAD was of 11 % and 5 %, respectively [22]. In our cohort, we found a prevalence of vasculopathy of 39.7%, and of CAD of 15.9 % among patients with severe acute hypertension (Table 2). Other factors contributing to pathogenesis of vasculopathy may also play a role also in pathogenesis of cancer [23], which ultimately led patients to surgery and ICU admission. Particularly, there is evidence that insulin resistance, hyperinsulinism and metabolic syndrome, which are all related to AH and vasculopathy, may contribute to cancer pathogenesis, due to insulin-induced endothelial hyperplasia [23]. Endothelial dysfunction may lead to and enhance the hypercoagulable state commonly observed in cancer patients [24], which further contributes to vasculopathy.

Chronic atrial fibrillation (CAF) was found to be a factor independently associated to acute severe hypertension in our study population (Table 1). Acute hypertension and CAF may share common pathogenesis, such as sustained increase in Renin Angiotensin Aldosterone system activity or inadequate anti-hypertensive treatment [25]. In critically ill surgical patients, perioperative autonomic hyperactivity, related to pain, hypothermia, hypovolemia, anemia, hypoxia or surgical trauma, may induce atrial fibrillation and acute hypertension [26].

Not surprisingly, severe acute hypertension was more frequent among patients in whom ICU admission was related to acute medical conditions (Table 2). Data from literature confirm that acute hypertension can complicate the course of many medical acute conditions which can lead to ICU admission, e.g. respiratory, renal or heart failure[27]. Moreover, many clinical entities requiring ICU admission, like acute cardiac arrhythmias, acute myocardial ischemia or acute renal failure, can also exacerbate or be precipitated by acute severe hypertension states [28]. Hypertension itself can be the clinical manifestation of some of these conditions, such as acute renal failure.

Outcome

In our patient population, severely hypertensive patients had longer ICU lengths of stay and higher rates of ICU- and in-hospital mortality (Table 5). It is important to outline that acute hypertension can exacerbate pre-existing organ failure, mainly cardiovascular or respiratory. International guidelines on perioperative cardiovascular management point out that optimal hypertensive treatment is important in order to reduce postoperative cardiovascular complications [29]. In critical care patients, either medical or surgical, optimal and patient tailored arterial pressure management could be linked to a better ICU outcome, in terms of reduced mortality and ICU length of stay.

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Conclusions

In a mixed medical-surgical ICU, hypertensive crises were common and patients tended to have more than one acute crisis during their ICU stay. Factors linked to acute hypertension were medical conditions leading to ICU-admission, older age, cigarette smoking, cancer diagnosis, CAD and chronic atrial fibrillation. Patients with severe acute hypertension had a worse outcome.

References

- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. (2003) Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Hypertension 42: 1206-1252.
- Pergolini MS (2009) The managment of hypertensive crises: a clinical Review. Clin Ter 160: 151-157.
- Elliott WJ (2003) Management of Hypertension Emergencies. Curr Hypertens Rep 5: 486-92.
- Goldberg ME, Larijani GE (1998) Perioperative hypertension. Pharmacotherapy 18: 911-914.
- De Gaudio AR, Chelazzi C, Villa G, Cavaliere F (2009) Acute severe arterial hypertension: therapeutic options. Curr Drug Targets 10: 788-798.
- Varon J (2008) Treatment of Acute Severe Hypertension. Current and newer agents. Drugs 68: 183-297.
- Martin JF, Higashiama E, Garcia E, Luizon MR, Cipullo JP (2004) Hypertensive crisis profile. Prevalence and clinical presentation. Arq Bras Cardiol 83: 131-136.
- Zampaglione B, Pascale C, Marchisio M, Cavallo-Perin P (1996) Hypertensive Urgencies and Emergencies: Prevalence and Clinical Presentation. Hypertension 27: 144-147.
- McVeigh GE, Bratteli CW, Morgan DJ, Alinder CM, Glasser SP, et al. (1999) Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: aging and arterial compliance. Hypertension 33: 1392-1398.
- 10. Taddei S (2009) Blood pressure through aging and menopause. Climacteric 12: S36-40.
- Sowers JR, Mohanty PK (1988) Autonomic nervous system function. J Hypertens Suppl 6: S49-54.
- 12. Tereshina EV (2009) Metabolic abnormalities as a basis for age-dependent diseases and aging? State of the art. Adv Gerontol 22: 129-138.
- Hamasaki H, Sato J, Masuda H, Tamaoki S, Isotani E, et al. (1997) Effect of Nicotine on the Intimal Hyperplasia after Endothelial Removal of the Rabbit Carotid Artery. Gen Pharmacol 28: 653-659.

- Edmiston JS, Flora JW, Scian MJ, Li G, Rana GS, et al. (2009) Cigarette smoke extract induced protein phosphorylation changes in human microvascular endothelial cells in vitro. Anal Bioanal Chem 394: 1609-1620.
- Mann SJ, James GD, Want RS, Pickering TG (1991) Elevation of ambulatory systolic blood pressure in hypertensive smokers. A Case- control study. JAMA 265: 2226-2228.
- Escalante CP, Weiser MA, Lam T, Ho V, Yeung SC (2005) Hypertension in cancer patients seeking acute care: an opportunity to intervene. Am J Med Sci 330: 120-127.
- Walther MM, Keiser HR, Linehan WM (1999) Pheochromocytoma: evaluation, diagnosis, and treatment. World J Urol 17: 35-39.
- Mauno V, Hannu K, Esko K (2008) Proinflammation and hypertension: a population-based study. Mediators Inflamm. 619704.
- Hingorani AD, Cross J, Kharbanda RK, Mullen MJ, Bhagat K, et al. (2000) Acute systemic inflammation impairs endothelium-dependent dilatation in humans. Circulation 102: 994-999.
- Chobanian AV, Alexander RW (1996) Exacerbation of atherosclerosis by hypertension. Potential mechanisms and clinical implications. Arch Intern Med 156: 1952-1956.
- Bennett PC, Silverman S, Gill P (2009) Hypertension and peripheral arterial disease. J Hum Hypertens 23: 213-215.
- 22. Katz JN, Gore JM, Amin A, Anderson FA, Dasta JF, et al. (2009) Practice patterns, outcomes, and end-organ dysfunction for patients with acute severe hypertension: the Studying the Treatment of Acute hyperTension (STAT) registry. Am Heart J 158: 599-606.
- Pollak M (2008) Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer 8: 915-928.
- 24. Kies MS, Posch JJ Jr, Giolma JP, Rubin RN (1980) Hemostatic function in cancer patients. Cancer 46: 831-837.
- 25. Go O, Rosendorff C (2009) Hypertension and atrial fibrillation. Curr Cardiol Rep 11: 430-5.
- 26. Kisner D, Wilhelm MJ, Messerli MS, Zünd G, Genoni M (2009) Reduced incidence of atrial fibrillation after cardiac surgery by continuous wireless monitoring of oxygen saturation on the normal ward and resultant oxygen therapy for hypoxia. Eur J Cardiothorac Surg 35: 111-115.
- Varon J (2007) Diagnosis and management of labile blood pressure during acute cerebrovascular accidents and other hypertensive crises. Am J Emerg Med 25: 949-959.
- 28. Gegenhuber A, Lenz K (2003) Hypertensive emergency and urgency. Herz 28: 717-724.
- Biagioli B, Catena G, Clementi G, Grillone G, Merli M, et al (2000) Raccomandazioni per la gestione perioperatoria del cardiopatico da sottoporre a chirurgia non cardiaca. Minerva Anestesiol 66: 85-104.