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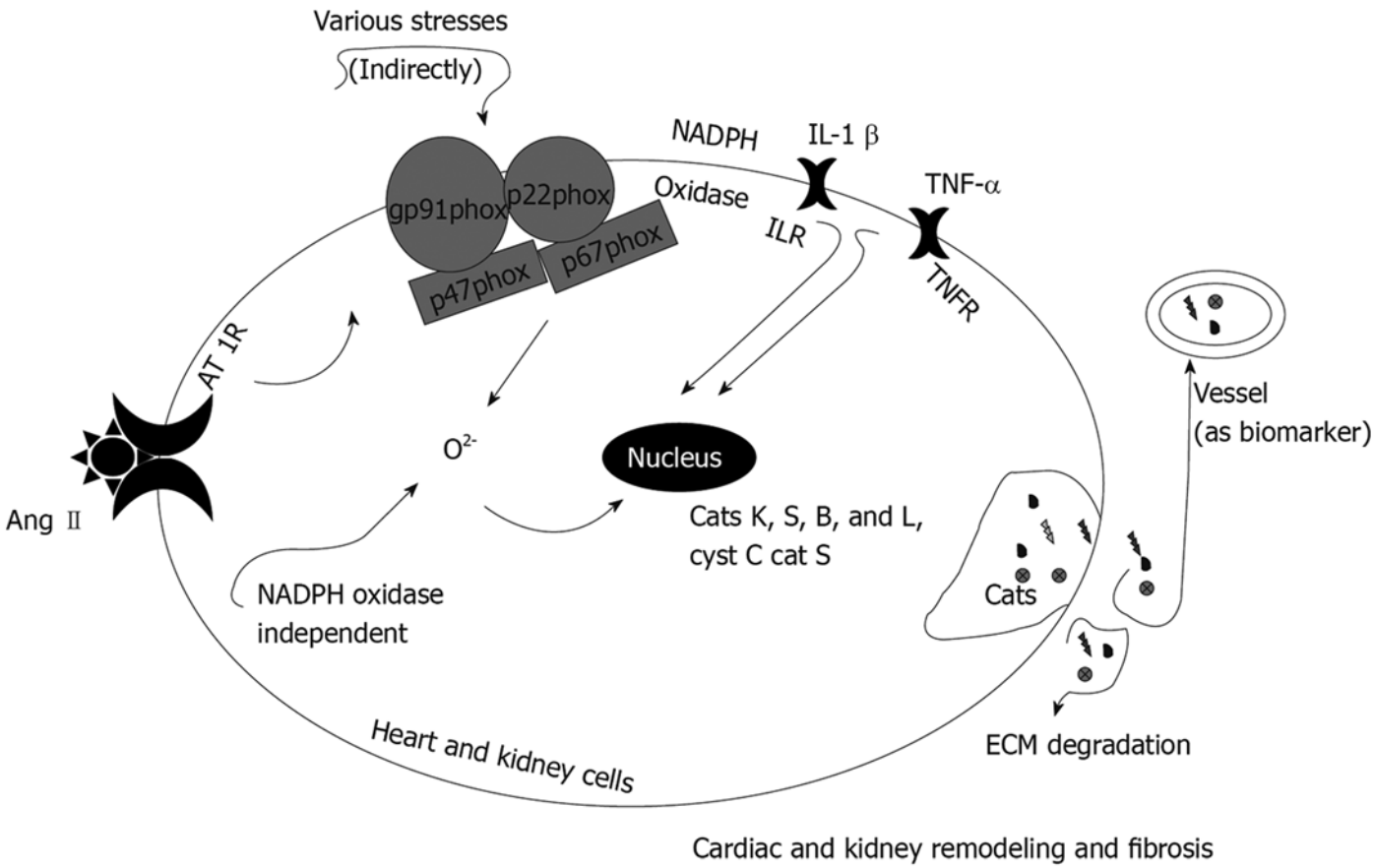

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Editorial Board of *World Journal of Hypertension*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjhypertens@wjgnet.com
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Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjhypertens@wjgnet.com
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EDITORIAL

Contribution of lysosomal cysteine proteases in cardiac and renal diseases

Damin Huang, Yang-Long Li, Xianwu Cheng

Damin Huang, Department of Cardiology, Xinhua Hospital (Chongming), School of Medicine, Shanghai Jiao Tong University, Shanghai 202150, China
Yang-Long Li, Department of Cardiology, The Longjing City Hospital, Longjing 133400, Jilin Province, China
Xianwu Cheng, Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan
Xianwu Cheng, Department of Cardiology, Yanbian University Hospital, Yanji 133000, Jilin Province, China
Xianwu Cheng, Department of Internal Medicine, Kyung Hee University Hospital, Seoul 130-701, South Korea
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Correspondence to: Xianwu Cheng, MD, PhD, Associate Professor of Cardiology, Department of Cardiology, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Japan. chengxw0908@yahoo.com.cn
Telephone: +81-52-7442364 Fax: +81-52-7442371
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Abstract

Cardiac and renal diseases (CRDs) are characterized by extensive remodeling of the extracellular matrix (ECM) architecture of the cardiorenal system. Among the many extracellular proteolytic enzymes present in cardiorenal cells and involved in ECM remodeling, members of the matrix metalloproteinase family and serine protease family have received the most attention. However, recent findings from laboratory and clinical studies have indicated that cysteine protease cathepsins also participate in pathogenesis of the heart and kidney. Deficiency and pharmacological inhibition of cathepsins have allowed their *in vivo* evaluation in the setting of pathological conditions. Furthermore, recent studies evaluating the feasibility of cathepsins as a diagnostic tool have suggested that the serum levels of cathepsins L, S and K and their endogenous inhibitor cystatin C have predictive value as biomarkers in patients with coronary artery disease and heart and renal failure. The goal of this review is to highlight recent discoveries regarding the contributions of cathepsins in CRDs, particularly hypertensive heart failure and proteinuric kidney disease.

Key words: Cysteine proteases; Cathepsins; Cystatin C; Extracellular matrix proteins; Cardiovascular disease; Inflammation

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CYSTEINE PROTEASE CATHEPSINS IN A NUTSHELL

Cysteine cathepsins are papain family members of the cysteine protease superfamily. In humans, 11 members have been identified: cathepsins B, C, F, H, K, L, O, S, V, W and X, all of which share a conserved active three-dimensional pocket formed with cysteine, histidine and asparagine residues. Cathepsins are synthesized as proenzymes. Procathepsin is formed after removal of the prepeptide during the passage to the endoplasmic reticulum. Cysteine cathepsins were originally identified as proteases acting in the

lysosome. More recent investigations have identified non-traditional roles for cathepsins in the extracellular space, as well as in the intracellular spaces[1-4]. These cathepsins have been demonstrated to play an important role in extracellular matrix (ECM) remodeling and have been implicated in the development and progression of cardiac and renal diseases (CRDs)[5-9]. Furthermore, evaluations of the feasibility of cathepsins as a diagnostic tool have revealed that the serum levels of several cathepsins seem to be promising biomarkers in the diagnosis of coronary artery disease, cardiac fibrosis and renal dysfunction[10-13].

The roles of cathepsins in atherosclerosis-based vascular disease and ischemic heart disease process have been covered by recent comprehensive reviews[14,15]. This review examines several issues in regard to cysteine cathepsin molecular function and participation in cardiorenal pathological processes, especially with respect to their potential application as diagnostic and/or prognostic markers and drug targets.

CATHEPSINS AND CYSTATIN C IN CRDS

Cardiac disease

More than a decade ago, cathepsin B, L and H were the first cathepsins identified in the myocardium of a rat model of acute myocardial infarction[16]. Crie and other groups reported a change in the cathepsin B protein and activity in cardiac injuries[17,18]. Failing human myocardium with dilated cardiomyopathy has been shown to overexpress cathepsin B mRNA and protein[19]. In studies by Cheng *et al*[6,7,20], it was reported that while normal cardiac tissues contained little or no cathepsin K or cathepsin S, these proteins were abundantly expressed in cardiac myocytes, macrophages, intracoronary smooth muscle cells (SMCs) and endothelial cells (ECs) of humans and animals with failing myocardium and hypertension. In addition to cardiac tissues, activated interstitial myofibroblasts have been shown to express the elastases cathepsin S and K in myxomatous heart valves[21]. Cell culture experiments have shown that proinflammatory mediators, including interleukin (IL)-1β or/and tumor-necrosis factor (TFN)-α, stimulate cathepsin S and cathepsin K gene expression and increased elastolytic and collagenolytic activity in neonatal cardiomyocytes, myxomatous valve-derived myofibroblasts and macrophages. This suggests that the inflammatory processes that prevail during cardiac remodeling locally increase the presence of the active form of these cathepsins. The ability of cardiomyocytes and macrophages to use cathepsins to degrade elastin and collagen support a role for these proteases in the cardiac wall and in valve alterations in humans and animals. Novel insights into cathepsin function have been gained by the generation and in-depth analysis of knockout and transgenic mice. Cathepsin L deficiency has been shown to result in cardiac chamber dilation and impaired cardiac function[22]. The human cathepsin L transgenic heart has been shown to exhibit a decrease in overload-induced hypertrophic response, apoptosis and fibrosis through blocking of the AKT/GSK3β signaling pathway in two models of aortic banding and angiotensin Ⅱ infusion[23]. Recently, *in vivo* and *in vitro* studies demonstrated that overexpression of cystatin C or exposing fibroblasts to cystatin protein resulted in an inhibition of cathepsin B and accumulation of collagens and fibronectin[24]. Although there have been numerous genetic studies on the functions of cathepsins, most of the molecular mechanisms underlying the roles of cathepsins in cardiac diseases remain unclear.

Kidney disease

Kidney cancer: The role of cysteine cathepsins in kidney cancer pathogenesis has been covered by a recent comprehensive review[25]. Here, we will focus on the role of cathepsins in several non-tumor-associated proteinuric kidney diseases, as described below.

Proteinuric kidney disease: More than a decade ago, it was reported that the levels of cathepsins B, L and H are altered in tubules of the rat kidney in response to injuries[26-29]. We reported that proximal tubular cells and podocytes of proteinuric failing kidneys contain much more cathepsin S protein than normal kidneys. In contrast, the tubular cells from the kidneys of patients with early stage diabetic and hypertensive hypertrophy show decreased activity of cathepsins B and L[28,30], suggesting that the roles of cathepsins in kidney disease might vary among the different cathepsins and different stages. On the other hand, cathepsin L is relatively well known to play a role in proteinuric kidney disease. In this regard, an article by Sever *et al*[2] provides new information of great interest. The authors demonstrate that cathepsin L deficiency impairs cleavage of dynamin at an evolutionarily conserved site, reducing the reorganization of the podocyte actin cytoskeleton and ameliorating proteinuria. Recent findings from *in vitro* experiments have shown that cathepsin L is involved in the podocyte migration coordinated by α3 integrin and degradation of the Rho GTPase regulator synaptopodin in podocytes[3,31]. In addition to podocytes and tubular cells, glomerular epithelial cells also express cathepsin L upon exposure to IL-4 and IL-13.

Pharmacological alternative to cathepsins and cystatin C in CRDs

Numerous cardiovascular drugs have been designed to target the expression and activity of cathepsins. Several recent groups, including our own, have demonstrated that the expression and activity of cathepsins S, K and L were increased in the failing myocardium and kidney of hypertensive animal models; these changes were targeted by the lipid-lowering and angiotensin Ⅱ receptor-blocking drugs olmesartan and statin *via* the reduction of inflammatory actions and the reduction of the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase-dependent superoxide production[7,20,32]. Simvastatin inhibited cardiac hypertrophy and fibrosis in apolipoprotein-deficient mice fed a high-fat diet by increasing peroxisome proliferator-activated receptor α and γ expressions and

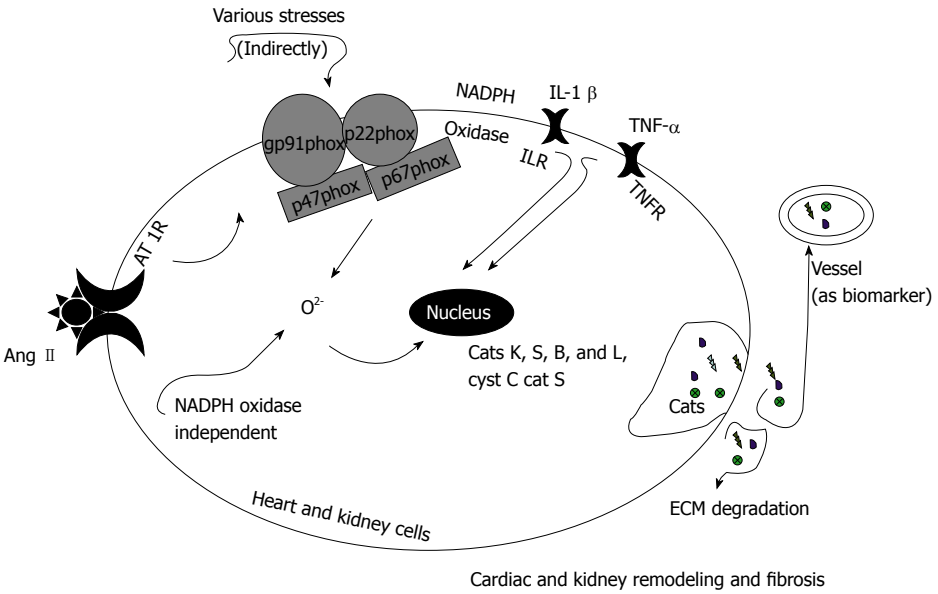

Figure 1 Roles of cathepsins and cystatin C in the pathogenesis of heart and kidney diseases. A schematic model of cathepsin regulation and function in cardiorenal cells is shown. Tissue and circulating cathepsins (Cats) were used as biomarkers for the diagnosis of cardiorenal disease. Ang I: Angiotensin Ⅱ; AT1R: Ang Ⅱ type 1 receptor; IL-1β: Interleukin-1β; TNF-α:Tumor necrosis factor-α; TNFR: TNF-α receptor; ILR: IL-1β receptor; ECM: Extracellular matrix; NADPH: Nicotinamide adenine dinucleotide phosphate.

reducing the expressions of matrix metalloproteinase (MMP)-9 and cathepsin S[33]. In addition, recent studies have shown that gallic acid also prevents lysosomal dysfunction by inhibiting increases in cathepsins B and D activity in myocardial injuries in animal models[34,35].

Circulating cathepsins or cystatin C as biomarkers for CRDs

Recent studies have evaluated the use of serum cathepsin levels as a diagnostic tool for heart and renal diseases. The most extensively described cysteine protease in renal insufficiency is the endogenous inhibitor cystatin C. Cystatin C is used to evaluate renal function and to detect the prevalence of dysfunction, particularly metabolic diseases[36]. Several human studies have indicated that serum cystatin C and cathepsin L are sensitive new predictors of potential kidney injury[13,37], particularly contrast-induced nephropathy. Interestingly, urinary cathepsin B activity is also increased in patients with membranous glomerulonephritis[38]. On the other hand, the feasibility of using cystatin C as a tool for predicting cardiac remodeling and clinical outcomes in patients with heart failure was recently explored. High levels of cystatin C were associated with an increased risk of heart failure, such an association may be limited to hypertensive individuals[39]. Manzano-Fernandez *et al*[12] reported that cystatin C can predict long-term outcomes in patients with acute heart failure. Although the data are still preliminary, these findings indicate that several cathepsins and/or cystatin C may serve as useful biomarkers in the diagnosis of CRDs.

CONCLUSION

Among cathepsins, cysteine protease cathepsins have been described to play a role in several heart and kidney diseases, including hypertensive heart failure and proteinuric kidney disease. Figure 1 shows an overview of potential regulations and functions for cathepsins in the pathogenesis of cardiorenal system. The data from laboratory and clinical studies showed that cysteine cathepsins B, K, L and S are mainly expressed in cardiorenal system cells, including cardiac myocytes, interstitial myofibroblasts, intracoronary SMCs and ECs, podocytes and tubular cells, and also to a lesser degree in CRDs-associated inflammatory macrophages. *In vitro* experiments revealed that, although these cells express negligible levels of cathepsins S, K and L, their incubation with inflammatory cytokines, such as IL-1β, TNF-α, and angiotensin Ⅱ, causes these cells to significantly express and secrete these cathepsins and to exhibit their collagenolytic and elastolytic activities. Several recent reports, related primarily to the remodeling of intracellular and extracellular proteins, have established an important role for cysteine in CRDs in genetically altered mice. Clinical findings have indicated a possible role for cathepsins as biomarkers in the diagnosis of CRDs and other diseases. Furthermore, pharmacological inhibition of cathepsin activity and expression as well as MMPs and SPs by several cardiovascular drugs has also shown protective effects in hypertensive heart failure and renal failure. We therefore propose that multiple proteases, including MMPs and SPs, work in concert during the initiation, progression and complications of CRDs.

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Anastasios K Kollias, MD, PhD, Hypertension Center, 3rd University Department of Internal Medicine, Sotiria Hospital, 152 Mesogion Avenue, Athens 11527, Greece

Xian-Wu Cheng, MD, PhD, Associate Professor, The Department of Cardiology, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Aichiken, Japan

Eric Lazartigues, PhD, FAHA, Assistant Professor, Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center - School of Medicine, 1901 Perdido Street, Room 5218, New Orleans, LA 70112, United States

Prasenjit Guchhait, PhD, Assistant Professor, Thrombosis Research Division, Cardiovascular Research Section, Department of Medicine, Baylor College of Medicine, One Baylor Plaza, N1319, Houston, TX 77030, United States

Murat Biteker, MD, Department of Cardiology, Haydarpasa Numune Education and Research Hospital, Kadıkoy, Istanbul 34750, Turkey

Pablo García de Frutos, PhD, Department of Cell Death and Proliferation, Head, Institute of Biomedical Research of Barcelona, c/ Rosellón 161, 6p, Barcelona E-08036, Spain

De-Pei Li, MD, Assistant Professor, Department of Critical Care, The University of Texas, MD Anderson Cancer Center, Houston, TX 77030, United States

Robert Joel Goldberg, PhD, Professor, Department of Quantitative Health Sciences, 7th Floor, ACCESS Building, University of MA Medical School, Worcester, MA 01655, United States

Andreas Daiber, PhD, Professor, Universitätsmedizin der JGU Mainz, Labor für Molekulare Kardiologie, Verfügungsgebäude für Forschung und Entwicklung 911, Raum 00349, Obere Zahlbacher Straße 63, 55101 Mainz, Germany

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Events Calendar 2012

January 11, 2012
Supporting the Challenge: Implementing the new NICE Hypertension Guidelines in Primary Care
BHS/PCCS/Takeda Workshop for Nurses & Pharmacists
Bristol, United Kingdom

February 8, 2012
BHS Hypertension & Cardiovascular Risk Spring Update for Nurses
Aberdeen Royal Infirmary,
Aberdeen, United Kingdom

February 10-12, 2012
Malaysian Society of Hypertension 9th Annual Scientific Meeting 2012
Kuala Lumpur, Malaysian

February 24, 2012
BHS Hypertension Masterclass
NICE Hypertension Guidelines: Essential Hypertension and Pregnancy
The Møller Centre, Churchill College,
Cambridge, United Kingdom

February 25- 28, 2012
Serbian Society of Hypertension 3rd International Meeting 2012
Belgrade, Serbia

March 3-5, 2012
South African Hypertension Society 17th Biennial Congress 2012
Cape Town, South Africa

March 14-18, 2012
9th Mediterranean Meeting on Hypertension and Atherosclerosis
Turkish Society of Hypertension and Atherosclerosis
Antalya, Turkey

March 22-25, 2012
2nd Latin America Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension 2012
Rio de Janeiro, Brazil

April 11-13, 2012
ICDHLSP 2012: International Conference on Diabetes, Hypertension, Lipids and Stroke Prevention
Venice, Italy

April 26 - 29, 2012
22nd Scientific Meeting of the European Society of Hypertension
Excel Centre,
London, United Kingdom

May 19 - 22, 2012
2012 American Society of Hypertension Annual Scientific Meeting & Exposition
Hilton New York,
NY, United States

June 21-24, 2012
10th International Pulmonary Hypertension Conference and Scientific Sessions 2012
Orlando,
FL, United States

July 9-12, 2012
3rd International Congress on Abdominal Obesity 2012
Quebec City, Canada

July 9-12, 2012
International Society for the Study of Hypertension in Pregnancy 18th World Congress 2012
Geneva, Switzerland

September 30 to October 4, 2012
Hypertension Sydney 2012
Sydney Convention and Exhibition Centre,
Sydney, Australia

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GENERAL INFORMATION

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Ocean International Center,
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Chaoyang District, Beijing 100025, China
E-mail: wjhypertens@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381891
Fax: +86-10-85381893

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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc*. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc*.
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc*.
Biology: *H. pylori*, *E coli*, *etc*.

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