ORIGINAL ARTICLE

Orthopaedic Surgeons' Cardiovascular Response During Total Hip Arthroplasty

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Abstract The literature contains limited and contradictory information regarding the amount of physical effort and/or emotional stress needed to perform surgery. We therefore investigated cardiovascular response to psychophysical stress in orthopaedic surgeons while they were performing surgery. We monitored 29 male orthopaedic surgeons from four university centers while they performed total hip arthroplasties. Changes in their cardiovascular parameters were recorded by ambulatory monitoring methods. Exercise stress testing of each participant was used as a control state. We compared the cardiovascular response during surgery to energy requirements of everyday activities. Preoperative and postoperative testing showed lower values of cardiovascular parameters than during physically less difficult parts of the operation; physically more difficult phases of the operation additionally increased the values of parameters. We concluded performing total hip arthroplasty increases surgeons' cardiovascular parameters because of psychologic stress and physical effort. Excitement of the cardiovascular system during total hip arthroplasty appears similar to the

M. Bergovec (⊠), D. Orlic Department of Orthopedic Surgery, Zagreb University School of Medicine and Clinical Hospital Centre Zagreb, Salata 7, HR-10000 Zagreb, Croatia e-mail: bergovec@gmail.com excitement during moderate-intensity daily activities, such as walking the dog, leisurely bicycling, or climbing stairs.

Introduction

There is no widely accepted agreement on the difficulty of performing surgery. Studies conducted during the last three decades that focused on monitoring and analyzing surwork had different findings and reached geons' contradictory conclusions [6, 7, 9, 11, 12, 15, 16, 22, 23, 30]. The studies were all stress-based and mostly analyzed cardiovascular parameters, such as heart rate and heart rate variability. In some of these studies, performing surgery was shown as "exhausting for the body" or "increasing heart rate to more than 150/minutes" [12, 15]. In others, "surgeons did not work physically remarkably hard nor demonstrated any obvious physiological signs of undue emotional stress" [6]. Some studies concluded experienced surgeons were well adapted to the particular stress, although surgeons rated their stress as "quite severe" and "lasting for hours" [6, 23]. Other studies used only heart rate variability as a surrogate parameter for increased sympathetic activity, ie, psychologic stress, while performing surgery [11, 12]. Several studies did not specify the operative procedure during which the monitoring was performed [6, 16, 22, 23], thus rendering the interpretation of emotional stress and especially physical demands impossible. Also, the number of participants-surgeons included in these studies was relatively small (two to 12; median, eight) [6, 7, 9, 11, 12, 15, 16, 22, 23, 30], diminishing the power of the studies and introducing the possibility of selection bias.

Orthopaedic surgeons use considerable muscle force while performing some types of operations (likely greater

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than most other surgical professions) and use heavy instruments, such as a mallet or bone saw, so they have one more factor for increased cardiovascular response in addition to psychologic stress. Thus, it seems there are major differences in cardiovascular response during various types of operative procedures [6, 7, 9, 11, 12, 15, 16, 22, 23, 30].

According to the Croatian Arthroplasty Register, joint arthroplasty incidence accounts for 26% of all orthopaedic operative procedures, meaning arthroplasty is orthopaedic surgeons' everyday job. Furthermore, this is one type of operation whose structure is well defined and likely similar across surgeons. Quantifying the difficulty of performing THA by measuring cardiovascular parameters may provide an objective measure of the average level of psychophysical demand imposed on orthopaedic surgeons during their everyday work, and on other surgical and medical specialists.

Our primary question was whether surgeons' cardiovascular responses (expressed as metabolic equivalents [METs]) increased at seven key points during THA and which parts of THA were most challenging from a cardiovascular response. We also asked what percentage of the surgeon's cardiovascular maximum occurred compared with a daily activity equivalent and whether the surgeons' cardiovascular responses depended on age, experience, or surgical approach.

Materials and Methods

We prospectively assessed 29 male orthopaedic surgeons (five professors, two assistant professors, three superintendents, 14 specialists, and five senior residents) from four orthopaedic university centers in Croatia who had agreed to participate with a response rate of 78%. From among those initially recruited, three participants were excluded: one participant had a prior cardiovascular incident and was at the time taking pharmacologic agents that could have influenced the cardiovascular results, one participant refused to participate, and one participant did not perform THA. The age range of the participants was 28 to 65 years. We divided participants into three age groups as follows: the youngest (< 35 years old, n = 7), middle-aged (36– 50 years old, n = 10), and the oldest (> 51 years old, n = 9). According to their surgical experience, the participants were classified as inexperienced (< 100 THAs, n = 9), moderately experienced (101–1000 THAs, n = 9), and very experienced (> 1000 THAs, n = 8).

The sample size calculation was performed with respect to the primary research question using G*Power software [13]. For repeated-measures analysis of variance with seven points of measurement, an alpha level of 0.05, a power of 80%, and an effect size of 0.2 or more (according to Cohen [10], an effect size of 0.14 or more can be considered large), we needed at least 26 participants in the study. The protocol was approved by the ethics committee, and every participant provided written informed consent before the beginning of the study.

During the first part of the investigation, participants were monitored while performing cementless THA. Other inclusion criteria were that the patient having surgery had no prior operation on that hip and the indication for surgery was osteoarthritis without any other hip problem that could make the standard operative procedure more difficult (ie, developmental hip malformation). Furthermore, it had to be the first operation for a participant that day, and the participant's subjective assessment of the operative procedure had to be medium difficulty (not more or less difficult than an average THA). All surgeries were performed in standard operating conditions (air conditioned operating room, with a temperature between 17° and 21° C) with a team of experienced assistants and nurses.

The participants used the standard surgical approach in their everyday use, an anteromedial approach with the patient in a lateral decubitus position (10 participants), or a lateral approach with the patient in a supine position (16 participants).

The implanted endoprostheses included an SPH-ST acetabular cup in 14 patients with a C2 femoral stem in 13 patients and an SL femoral stem in one patient (Lima-Lto SpA Medical Systems, Villanova, Italy); a HITM acetabular cup with a UNITM femoral stem in nine patients (Plus Orthopedics AG, Rotkreuz, Switzerland); and a Trilogy[®] Acetabular System acetabular cup with a VerSys[®] Hip System Enhanced Taper femoral stem in three patients (Zimmer, Inc, Warsaw, IN).

While performing surgery, participants were monitored by an ambulatory blood pressure monitor (90217 ABP monitor; Spacelabs Medical, OSI Systems, Inc, Redmond, WA) and an ambulatory Holter ECG digital recorder (Medilog MR63; Oxford Instruments, Abington, UK), which were attached at least 30 minutes before and removed a minimum of 30 minutes after surgery. Monitored parameters were systolic and diastolic blood pressure, heart rate, rate-pressure product (product of heart rate and systolic blood pressure), arrhythmias, and signs of possible ischemic or other cardiovascular disease.

When monitoring started, one observer (MB) documented every action and part of the surgery and synchronized it with the time on the monitors. Monitoring time and data were divided into seven precisely defined key points of the surgery (Table 1) according to the surgeon's activity for proper evaluation of cardiovascular response during each part of the procedure.

According to the surgeon's activity and the surgical instruments he used, key points were considered as either physically less demanding parts of the operation (ie, using

Table 1.	Key points	of monitoring	orthopaedic	surgeons	while they are	performing THA

Key poir	at Description
1	Preoperative time, 30 minutes before beginning the operation
2	Beginning of the operation: skin incision, preparation of anatomic structures
3	Exposure of the hip, femoral head subluxation, osteotomy of the femoral neck with an oscillating saw, removing the femoral head
4	Preparing acetabulum, reaming acetabulum, inserting acetabular endoprosthetic part
5	Preparing femur, rasping femoral canal, inserting femoral endoprosthetic part, endoprosthetic reposition
6	Suturing, wound closure, end of the operation
7	Postoperative time: up to 30 minutes after ending the operation

scalpel, forceps, scissors, needle holder, and so on) or physically more demanding parts of the operation (ie, using a mallet, osteotome, oscillating saw, bone cutting forceps, bone rongeur, acetabular reamer, femoral rasp, etc).

The energy expenditure (oxygen uptake) required to produce rate-pressure product equal to that at each key point for each participant was determined by exercise stress testing according to the Bruce protocol, a multilevel, treadmill, symptom-limited, maximal progressive exercise test [4, 19], performed a few weeks after monitoring of the surgery. We computed METs to reflect the energy requirements for psychophysical activities during different parts of THA. According to exercise testing results and MET standards, defined as the energy expenditure and caloric requirement at rest (approximately 3.5 mL oxygen uptake/kg body weight/minute [4]), we calculated METs for each key point of the operation. We also compared our results obtained during THA with the standard METs during daily activities [2, 3, 14, 17, 24].

Data are shown as mean with 95% confidence interval (95% CI) and the level of significance in comparison with postoperative rest and the peak-exciting part of the operation. We used parametric procedures as the parameter distribution was normal (Kolmogorov-Smirnov test). Changes in systolic and diastolic blood pressure, heart rate, rate-pressure product, and MET were analyzed with repeated-measures analysis of variance. Partial η^2 was greater than 0.7 for all analyzed parameters, indicating large and significant differences between the values [21]. Analysis was performed with SPSS 13.0 (SPSS Inc, Chicago, IL), and the significance level was set at p < 0.05.

Results

Blood pressure, heart rate, and rate-pressure product increased but varied during the seven key points. Metabolic equivalents also varied during the seven key points (p < 0.001, Wilks' lambda = 0.18, F[6,20] = 14.9, partial $\eta^2 = 0.82$).

Blood pressure, heart rate, and rate-pressure product reached their highest values during the implantation of the femoral endoprosthesis part of the operation (Key Point 5) and were increased (p < 0.001 for all) at this key point compared with their lowest values during the total period of measurement (Table 2). Metabolic equivalents also were highest during the femoral endoprosthetic part of the operation (Key Point 5) and the lowest during the postoperative rest time (Key Point 7) (Fig. 1). Key Point 5 was also the most challenging part of the operation when comparing maximum values of rate-pressure product during exercise testing with the maximum rate-pressure product during the operation, requiring 41.5% (95% CI, 34.8%-48.1%) of the surgeon's cardiovascular maximum. Systolic blood pressure, heart rate, and rate-pressure product were higher ($p \le 0.008$, $p \le 0.003$, and p < 0.001, respectively) during the operative steps (Key Points 2-6) than during the postoperative 30-minute rest (Key Point 7). We observed no differences in systolic or diastolic blood pressure between the most difficult part of THA (Key Point 5) and less difficult parts of THA (Key Points 3 and 6). Heart rate and ratepressure product were higher (p < 0.001 and $p \le 0.031$, respectively) during the most difficult part of THA when compared with less difficult parts of THA.

When compared with everyday activities, energy requirements for performing THA were similar to moderateintensity physical activity (Fig. 1). Walking at a slow pace, making a bed, playing a musical instrument, or sweeping a floor were activities that matched energy requirements from surgeons in the 30-minute period before and after performing THA (< 2.5 METs). Slow dancing, fishing, or walking the dog matched physically less-demanding parts of THA (2.5-3 METs), whereas water aerobics, golf (when not carrying clubs), walking at an average pace, leisurely bicycling, climbing stairs, and table tennis matched physically more demanding parts of THA (3-4 METs). Performing THA was far from being a vigorous physical activity, such as skating, downhill skiing (> 6 METs), jogging, singles tennis (> 7 METs), soccer, rowing (> 8 METs), running, or rope jumping (> 10 METs).

Cardiovascular parameter	THA key point*							p Value⁺	$p Value^{\dagger} p Value^{\ddagger}$
	1	2	3	4	5	6	7		
Systolic blood pressure (mm Hg) 139 (134–144)	139 (134–144)	142 (137–148)	148 (143–154)	147 (141–153)	151 (144–158)	148 (143–154) 147 (141–153) 151 (144–158) 142 (136–147) 129 (124–134) ≤0.008	129 (124–134)	≤0.008	1.000
Diastolic blood pressure (mm Hg) 94 (90–98)	94 (90–98)	92 (88–96)	95 (90–99)	94 (90–97)	96 (92–100)	92 (89–96)	85 (82–89)	0.271	1.000
Heart rate (beats/min)	81 (75–87)	85 (78–91)	94 (87–102)	100 (91–109)	106 (98–114)	97 (89–105)	84 (79–90)	≤0.003	<0.001
Rate-pressure product (×1000)	11.4 (10.4–12.4)	11.4 (10.4 - 12.4) 12.1 (10.9 - 13.3) 14.0 (12.7 - 15.4) 14.7 (13.1 - 16.4) 16.1 (14.5 - 17.6) 13.7 (12.4 - 14.9) 10.9 (10.1 - 11.7) <0.001	14.0 (12.7–15.4)	14.7 (13.1–16.4)	16.1 (14.5–17.6)	13.7 (12.4–14.9)	10.9 (10.1–11.7)	<0.001	≤0.031

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Fable 2. Values of monitored cardiovascular parameters in orthopaedic surgeons while they are performing THA

There was no difference in cardiovascular response while performing THA according to surgeon's prior operative experience or seniority. Surgical approach also did not affect the results. Overall, we found no extrinsic factors that influenced surgeons' cardiovascular response.

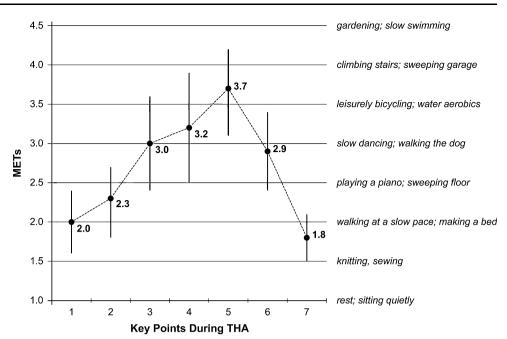
Seven participants had cardiac arrhythmias during Holter monitoring time, which was an unexpected finding. Arrhythmias in six participants were not considered clinically relevant: four of them had five or fewer isolated supraventricular extrasystoles, and two had five or fewer isolated ventricular extrasystoles. One participant had 17 ventricular extrasystoles, one bigeminy, and one supraventricular extrasystole and was referred for further cardiologic evaluation. We found no correlation between arrhythmias and part of the operative procedure or the magnitude of the cardiovascular response. No signs of ischemic cardiac disease or other cardiac problems were observed.

Discussion

Orthopaedic surgeons perform psychophysically demanding operations, such as THA, every day. However, there is no conclusion regarding how demanding such operations are with respect to psychophysical effort required from the surgeon. We determined energy requirements and cardiovascular response to physical effort and psychologic stress during THA and found that the MET level of the most demanding part of the operation equaled energy requirements of a moderate-intensity daily activity, such as leisurely bicycling, and required approximately 40% of surgeons' cardiovascular maximum, which did not vary with respect to surgeons' age, operative experience, or surgical approach.

There are several limitations to our study. Physical activity and psychologic stress increase cardiovascular parameters and we could not differentiate the effects of physical effort from the effects of psychologic stress on cardiovascular response. This should be considered when interpreting our data. Furthermore, we did not measure participants' cardiovascular response to various other activities or establish individual baseline cardiac status, including the presence of arrhythmias, which were an unexpected finding. In future studies, Holter monitoring for 24 hours before monitoring during surgery could provide more insight into the cardiovascular response and level of stress in individual orthopaedic surgeons. Finally, we analyzed the first operations of the day that were moderately difficult according to participants' subjective assessment and not aggravated by any additional operative or other complications. Certainly, surgeons perform more difficult operations and more than one operation a day. In cases where complications develop or where the surgeon

Fig. 1 The METs of orthopaedic surgeons while they are performing THA are shown. Results are shown as means and 95% CIs. The daily activities with equivalent MET values (energy requirements) are shown on the right side.



already has performed several operations, the energy requirements presumably would be higher.

Various factors increase surgeons' psychophysical stress in the operating room, such as increased work of breathing resulting from hyperventilation, airway resistance imposed by surgical masks, the heat and moisture under the masks, occlusive garments, and radiation of operating room lights [12]. However, stress rate for orthopaedic surgeons during surgery could be decreased because of improvements in hip designs, surgical techniques, fixation methods, and prophylactic therapies [8]. However, patient expectations of a perfect operative result because of modern technology could lead to a higher stress level.

In some studies, heart rate variability was used to evaluate sympathovagal balance in surgeons while performing surgery [7, 11, 12]. We did not use this parameter because of considerable controversies regarding heart rate variability in stress analysis. Although some authors suggest heart rate variability is the most objective and reliable noninvasive methodology available for accessing psychologic stress [20, 28, 29], others claim it is a gross oversimplification because results of reliability studies are heterogeneous and depend on many factors, which is why the analysis of heart rate variability as a direct window to autonomic tone is problematic [25, 27] and contains as much prognostic information as a simple heart rate measurement [1, 18, 31].

Yamamoto et al. concluded intraoperative stress decreases with experience [30]. Our results did not confirm this finding. A possible explanation could lie in the difference in physical strength between older and younger surgeons. Older and more experienced surgeons may be less psychologically stressed than their younger and less experienced colleagues, but they also have less muscular strength and therefore invest more physical effort.

Psychologic stress is widely accepted as a risk factor for development of coronary heart disease, hypertension, cardiac arrhythmias, blood lipid disturbances, and diabetes mellitus [31]. It could be the reason why, when considering cardiovascular mortality in the medical profession, surgeons seem at especially high risk of dying of ischemic heart disease [5, 26]. However, recreational physical activity is considered beneficial for cardiovascular status. With respect to cardiovascular parameters, ie, metabolic demands on the heart, performing operations that equal moderate-intensity physical activity may be compared with recreational, leisurely bicycling. The psychophysical condition of the orthopaedic surgeons while performing THA or other physically demanding procedures could be compared with the psychophysical condition of sportsmen during a competitive challenge; increase in cardiovascular parameters in either case results from physical activity and psychologic stress.

The methods we used in our study could be useful in additional research into energy requirements during different surgeries and in other medical specialties. Although they may not be used in evaluating cardiovascular demands as possible cardiovascular risk factors, our methods could be used in determining the level of psychophysical difficulty of a physician's job. Such data might ultimately be useful in assessing the relative roles of stress in various specialties. Acknowledgments We thank the orthopaedic surgeons who participated in this study. We also thank Prof Mijo Bergovec for expertise in cardiovascular parameters analysis; Dr Mirjana Jembrek-Gostovic for conceding cardiovascular equipment; Dr Marija Hocevar, Dr Viktor Persic, and Dr Neven Varljen for performing exercise testing; and Prof Darko Hren for statistical expertise. We are grateful to Prof Ana Marusic, *Croatian Medical Journal* Editor-in-Chief, for critical reading of the manuscript.

References

- Abildstrom SZ, Jensen BT, Agner E, Torp-Pedersen C, Nyvad O, Wachtell K, Ottesen MM, Kanters JK, BEAT Study Group. Heart rate versus heart rate variability in risk prediction after myocardial infarction. J Cardiovasc Electrophysiol. 2003;14:168–173.
- Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc.* 1993;25:71–80.
- Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* 2000;32(9 suppl):S498–504.
- American Thoracic Society/American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167:211–277.
- Arnetz BB, Andreasson S, Strandberg M, Eneroth P, Kallner A. Comparison between surgeons and general practitioners with respect to cardiovascular and psychosocial risk factors among physicians. *Scand J Work Environ Health.* 1988;14:118–124.
- Becker WG, Ellis H, Goldsmith R, Kaye AM. Heart rates of surgeons in theatre. *Ergonomics*. 1983;26:803–807.
- Böhm B, Rötting N, Schwenk W, Grebe S, Mansmann U. A prospective randomized trial on heart rate variability of the surgical team during laparoscopic and conventional sigmoid resection. *Arch Surg.* 2001;136:305–310.
- Branson JJ, Goldstein WM. Primary total hip arthroplasty. AORN J. 2003;78:947–953, 956–969; quiz 971–974.
- Coelho JC, Precoma D, Campos AC, Marchesini JB, Pereira JC. Twenty-four-hour ambulatory electrocardiographic monitoring of surgeons. *Int Surg.* 1995;80:89–91.
- Cohen J. Statistical Power Analysis for Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
- Czyzewska E, Kiczka K, Czarnecki A, Pokinko P. The surgeon's mental load during decision making at various stages of operations. *Eur J Appl Physiol Occup Physiol.* 1983;51:441–446.
- Demirtas Y, Tulmac M, Yavuzer R, Yalcin R, Ayhan S, Latifoglu O, Atabay K. Plastic surgeon's life: marvelous for mind, exhausting for body. *Plast Reconstr Surg.* 2004;114:923–931; discussion 932–933.
- Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39:175–191.
- Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Piña IL, Rodney R,

Simons-Morton DA, Williams MA, Bazzarre T. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;104:1694–1740.

- Foster GE, Evans DF, Hardcastle JD. Heart-rates of surgeons during operations and other clinical activities and their modification by oxprenolol. *Lancet.* 1978;1:1323–1325.
- Goldman LI, McDonough MT, Rosemond GP. Stresses affecting surgical performance, learning: I: correlation of heart rate, electrocardiogram, and operation simultaneously recorded on videotapes. J Surg Res. 1972;12:83–86.
- Jétte M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol.* 1990;13:555–565.
- Karcz M, Chojnowska L, Zareba W, Ruzyllo W. Prognostic significance of heart rate variability in dilated cardiomyopathy. *Int J Cardiol.* 2003;87:75–81.
- Lear SA, Brozic A, Myers JN, Ignaszewski A. Exercise stress testing: an overview of current guidelines. *Sports Med.* 1999;27:285–312.
- McCraty R, Atkinson M, Tiller WA, Rein G, Watkins AD. The effects of emotions on short-term power spectrum analysis of heart rate variability. *Am J Cardiol.* 1995;76:1089–1093.
- Pallant J. SPSS Survival Manual: A Step by Step Guide to Data Analysis using SPSS Version 12. 2nd ed. New York, NY: Open University Press; 2004.
- Payne RL, Rick JT. Heart rate as an indicator of stress in surgeons and anaesthetists. J Psychosom Res. 1986;30:411–420.
- Payne RL, Rick JT, Smith GH, Cooper RG. Multiple indicators of stress in an 'active' job: cardiothoracic surgery. J Occup Med. 1984;26:805–808.
- 24. Physical Activity and Health: A Report of the Surgeon General. US Department of Health and Human Services, Centers for Disease Control and Prevention; 1996. Available at: http:// wonder.cdc.gov/wonder/PrevGuid/m0042984/m0042984.asp. Accessed September 10, 2007.
- Pieper SJ, Hammill SC. Heart rate variability: technique and investigational applications in cardiovascular medicine. *Mayo Clin Proc.* 1995;70:955–964.
- Rimpelä AH, Nurminen MM, Pulkkinen PO, Rimpelä MK, Valkonen T. Mortality of doctors: do doctors benefit from their medical knowledge? *Lancet.* 1987;1:84–86.
- Sandercock GR, Bromley PD, Brodie DA. The reliability of short-term measurements of heart rate variability. *Int J Cardiol.* 2005;103:238–247.
- Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. *Am Heart J.* 1994;127:1376–1381.
- Task Force of the European Society of Cardiology, the North American Society of Pacing Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation*. 1996;93:1043–1065.
- Yamamoto A, Hara T, Kikuchi K, Hara T, Fujiwara T. Intraoperative stress experienced by surgeons and assistants. *Ophthalmic Surg Lasers*. 1999;30:27–30.
- Zipes DP, Libby P, Bonow RO, Braunwald E. (eds). Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005.