Clinical Investigation

Comparison of Perioperative and Postoperative Outcomes Among 3 Left Atrial Incisions: Conventional Direct, Transseptal, and Superior Septal Left Atriotomy

Estelle Démoulin¹; Dionysios Adamopoulos, MD²; Tornike Sologashvili, MD¹; Mathieu van Steenberghe, MD, PhD¹; Jalal Jolou, MD¹; Haran Burri, MD, PhD²; Christoph Huber, MD, PhD¹; Mustafa Cikirikcioglu, MD, PhD¹

¹Division of Cardiovascular Surgery, Department of Surgery, University Hospitals of Geneva, Geneva, Switzerland
²Division of Medical Specialties, University Hospitals of Geneva, Geneva, Switzerland



Abstract

Background: Achieving optimal exposure of the mitral valve during surgical intervention poses a significant challenge. This study aimed to compare perioperative and postoperative outcomes associated with 3 left atriotomy techniques in mitral valve surgery—the conventional direct, transseptal, and superior septal approaches—and assess differences during the surgical procedure and the postoperative period.

Methods: Inclusion criteria were patients undergoing mitral valve surgery from January 2010 to December 2020, categorized into 3 cohorts: group 1 (conventional direct; n = 115), group 2 (transseptal; n = 33), and group 3 (superior septal; n = 59). To bolster sample size, the study included patients undergoing mitral valve surgery independently or in conjunction with other procedures (eg, coronary artery bypass grafting, aortic-tricuspid surgery, or maze procedure).

Results: No substantial variance was observed in the etiology of mitral valve disease across groups, except for a higher incidence of endocarditis in group 3 (P = .01). Group 1 exhibited a higher frequency of elective surgeries and isolated mitral valve procedures (P = .008), along with reduced aortic clamping and cardiopulmonary bypass durations (P = .002). Conversely, group 3 patients represented a greater proportion of emergency procedures (P = .01) and prolonged intensive care unit and hospital stays (P = .001). No significant disparities were detected in terms of permanent pacemaker implantation, postoperative complications, or mortality among the groups.

Conclusion: Mitral valve operations that employed these 3 atriotomy techniques demonstrated a safe profile. The conventional direct approach notably reduced aortic clamping and cardiopulmonary bypass durations. The superior septal method was primarily employed for acute pathologies, with no significant escalation in postoperative arrhythmias or permanent pacemaker implantation, although these patients had prolonged intensive care unit and hospital stays. These outcomes may be linked to the underlying pathology and nature of the surgical intervention rather than the incision method itself.

Keywords: Mitral valve; perioperative period; complications; artificial pacemaker

Introduction

or more than 5 decades, mitral valve surgery has stood as a foundational cardiac procedure worldwide, owing
its prominence to advancements in open-heart surgical techniques.¹ Predominantly, mitral valve surgeries are executed through a median sternotomy incision, using direct left atriotomy exposure, often referred to as the

Citation: Démoulin E, Adamopoulos D, Sologashvili T, van Steenberghe M, Jolou J, Burri H, Huber C, Cikirikcioglu M. Comparison of perioperative and postoperative outcomes among 3 left atrial incisions: conventional direct, transseptal, and superior septal left atriotomy. *Tex Heart Inst J*. 2024;51(1):e238162. doi:10.14503/24-8162.

Corresponding author: Estelle Démoulin, 134 Chemin de la Montagne, 1224 Chêne-Bougeries, Switzerland (demoulinestelle@gmail.com)

conventional direct incision. The inherent anatomical positioning of the mitral valve, however, vertically distant from the sternum, poses a major challenge—one that is particularly pronounced in acute pathologies where left atrial dilation is absent.

To address this challenge, alternative approaches for mitral valve exposure, including transseptal and superior septal left atriotomy, have been developed. These methods aim to overcome limitations by facilitating a broader operative field.

The present study aimed to juxtapose the perioperative and postoperative outcomes associated with these 3 distinct incisions among patients undergoing mitral valve surgery, both independently and in conjunction with related procedures.

Patients and Methods

Between January 2010 and December 2020, a total of 485 adult patients underwent mitral valve surgery within the Division of Cardiovascular Surgery at the University Hospital of Geneva. For this study, 207 patients were included and categorized into 3 distinct groups:

- Group 1 (n = 115) underwent conventional direct left atriotomy.
- Group 2 (n = 33) underwent transseptal left atriotomy.
- Group 3 (n = 59) underwent superior septal left atriotomy.

To augment the sample size, all patients who underwent surgical interventions targeting mitral valve pathology, either independently or in combination with associated procedures, were included. Approval for the study protocol was obtained from SwissEthics, the local ethics committee, on July 6, 2021 (2021-00548).

This retrospective observational study entailed the analysis of (1) patients' demographic characteristics (2) preoperative and postoperative electrocardiographic findings; (3) perioperative metrics, such as durations of aortic clamping and cardiopulmonary bypass; and (4) postoperative outcomes, including permanent pacemaker implantation, revisions resulting from bleeding, incidence of infection, cardiogenic shock, pulmonary complications, and lengths of stay in both the intensive care unit (ICU) and the hospital (the entire hospital stay, from the day of the operation). Patient demographic and clinical data were sourced from patient records, while operative reports provided the perioperative information.

Key Points

- Noticeable disparities were observed in the postoperative period, specifically regarding the duration of hospital stays among the 3 distinct atriotomy approaches.
- The selection of a specific atriotomy was found to be customized based on preoperative data, indicating a personalized approach in the choice of surgical technique.
- There were no observed variations in preoperative and postoperative rhythms linked to the particular atriotomy performed, suggesting a consistent pattern in rhythm outcomes irrespective of the chosen approach.

Abbreviations and Acronyms

ICU intensive care unit

Statistical Analysis

Statistical analysis was conducted using SPSS, version 25, software (IBM SPSS Statistics). Continuous variables following a normal distribution were presented as mean (SD). The normality of data distribution was evaluated through visual inspection of histograms for continuous variables. Categorical variables were expressed as absolute numbers and percentages. A significance threshold of P < .05 was applied for determining statistical significance.

Parametric and nonparametric statistical methods were selected based on the normality distribution of comparative variables. Categorical variables were analyzed using the χ^2 test for comparison among the groups. For continuous variables displaying normal distribution, analysis of variance was employed. In cases where the distribution deviated from normality, the Kruskal-Wallis test (a nonparametric equivalent to 1-way analysis of variance) was used. Subsequently, to assess individual differences between groups, post hoc tests were conducted, with Bonferroni correction applied for multiple comparisons.

Surgical Atriotomies

The conventional direct incision is anatomically situated anterior to the right pulmonary veins and posterior to the interatrial groove. Its primary use occurs in conventional operations through sternotomy and in minimally invasive mitral valve procedures executed through a right anterior thoracotomy. Although the conventional direct incision offers excellent visibility for operations conducted through an anterior right thoracotomy because of its linear access, challenges arise when exposing the mitral valve during procedures performed through a median sternotomy, particularly in cases involving acute pathologies. This incision's anterior positioning may impede optimal visualization of the mitral valve, posing a difficulty in such scenarios.

The transseptal left atriotomy involves a dual-incision approach. Initially, a right atriotomy is performed parallel to the atrioventricular groove, followed by an incision in the interatrial septum, situated below the lower half of the fossa ovalis. This incision technique offers superior exposure compared with the conventional direct incision, particularly when accessed through a median sternotomy. Moreover, it grants the opportunity to address pathologies involving both the mitral and tricuspid valves simultaneously.

The superior septal left atriotomy involves a 2-step incision process. First, a right atriotomy is executed, followed by the continuation of the cephalic aspect upward toward the base of the atrial appendix, ultimately reaching the highest point of the atrial septum. Then, an incision is made below the lower section of the fossa ovalis, extending to the apex of the initial incision. The conjunction of these incisions is then further extended toward the apex of the left atrium. A theoretical drawback of this approach, however, is the potential for atrial dysrhythmia resulting from the incision into the sinus node artery.

Results

Preoperative Demographic Characteristics

Among the cohort of 207 patients, 125 (60.4%) were male and 82 (39.6%) were female. Notably, no statistically significant difference was observed in terms of sex distribution (P = .34). Emergency operations totaled 33, with a notable trend indicating a higher prevalence of superior septal left atriotomy in these urgent cases (P = .01). Regarding the primary surgical indications, no overall differences were discerned, except in cases of endocarditis, where a preference for superior septal left atriotomy was evident (P = .01), as detailed in Table I.

Perioperative Characteristics

No statistically significant differences were observed in the choice between valvuloplasty (P = .08) and valve replacement (P = .08). Notably, a subset of patients initially scheduled for valvuloplasty required an intraoperative transition to valve replacement. This scenario occurred in 5 patients within group 1 and 1 patient within group 3. Isolated mitral valve procedures exhibited a predilection for the use of conventional direct left atriotomy over the alternative incision types (P = .008).

Intraoperative data for the 3 groups are outlined in Table I. Specifically, when employing the conventional direct incision, shorter durations of cardiopulmonary bypass and aortic clamping were noted. Understandably, cardiopulmonary bypass and aortic clamping times were extended when associated procedures were performed concurrently. Analysis of operating times in isolated mitral valve operations among the groups revealed notable differences. For 61 patients in group 1, the mean (SD) cardiopulmonary bypass time was 85.6 (41.5) minutes, and aortic cross-clamp time was 60.9 (29.4) minutes. For 9 patients in group 2, the mean (SD) cardiopulmonary bypass time was 117.0 (42.1) minutes, and aortic cross-clamp time was 77.7 (16.8) minutes. For 21 patients in group 3, the mean (SD) cardiopulmonary bypass time was 112.3 (49.8) minutes, and aortic cross-clamp time was 76.1 (32.2) minutes. Because of the smaller sample size in group 2 and the group's non-normal distribution, the Kruskal-Wallis test was used. Cardiopulmonary bypass time was statistically significantly shorter in group 1 than in group 3 (P = .02). Although a tendency toward shorter aortic cross-clamp times in group 1 than in groups 2 and 3 was observed, this trend did not reach statistical significance (P = .06).

Postoperative Characteristics

No statistically significant differences were identified in postoperative rhythms or postoperative complications among the 3 groups (Table II), although discernible disparities were noted in the duration of ICU stay and total in-hospital days. Specifically, group 3 exhibited longer durations than did group 1, as illustrated in Table I.

Permanent Pacemaker Implantation

A trend was observed indicating a higher occurrence of permanent pacemaker implantation in group 3 than in group 1 (P = .06). Recognizing that the maze procedure and tricuspid surgery might influence and potentially contribute to permanent pacemaker implantation, these cases were excluded from the analysis. With these exclusions, no significant differences were found among the 3 groups (P = .32).

Parameter	Group 1 (n = 115)	Group 2 (n = 33)	Group 3 (n = 59)	P value ^a
Preoperative				
Age, mean (SD), y	63.0 (14.4)	58.5 (19.2)	67.1 (14.7)	.04
Male sex, No. (%)	74 (64.3)	20 (60.6)	31 (52.5)	.34
Emergency operation, No. (%)	11 (9.6)	6 (18.2)	16 (27.1)	.01
Reason for surgery, No. (%)				
Insufficiency	92 (80)	24 (72.7)	38 (64.4)	.08
Endocarditis	8 (7.0)	3 (9.1)	13 (22.0)	.01
Stenosis	7 (6.1)	5 (15.2)	6 (10.2)	.23
Perioperative outcomes				
Isolated mitral valve surgery, No. (%)	61 (53.0)	9 (27.3)	21 (35.6)	.008
With associated procedures, No. (%)	54 (47.0)	24 (72.7)	38 (64.4)	.008
Cardiopulmonary bypass time, mean (SD), min	95.2 (39.1)	124.5 (43.3)	120.8 (49.1)	.001
Aortic cross-clamping time, mean (SD), min	67.8 (29.6)	84.1 (31.6)	83.3 (34.2)	.002
Valvuloplasty, No. (%)	82 (71.3)	17 (51.5)	36 (61.0)	.08
Valve replacement, No. (%)	33 (28.7)	16 (48.5)	23 (39.0)	.08
Postoperative outcomes				
Pulmonary complications, No. (%)	16 (13.9)	5 (15.2)	13 (22.0)	.19
Cardiogenic shock, No. (%)	2 (1.7)	2 (6.1)	2 (3.4)	.46
Neurologic complication, No. (%)	2 (1.7)	0 (0.0)	0 (0.0)	.69
Major bleeding, No. (%)	16 (14.0)	4 (12.1)	4 (6.8)	.39
Intensive care unit length of stay, mean (SD), d	4.2 (3.6)	5.0 (3.1)	7.1 (6.4)	.001
Hospital length of stay, mean (SD), d	15.1 (6.1)	17.0 (7.0)	19.6 (11.6)	.003
Died, No. (%)	6 (5.2)	3 (9.1)	4 (6.8)	.42
Permanent pacemaker implantation, No. (%)	5 (4.3)	0 (0.0)	7 (11.9)	.06
Permanent pacemaker implantation, excluding tricuspid surgery and maze procedure, No. (%)	2 (2.4)	0 (0.0)	3 (7.5)	.32

TABLE I. Preoperative, Perioperative, and Postoperative Parameters

 $^{a}P < .05$ was considered statistically significant.

Parameter	Group 1 (n = 115)	Group 2 (n = 33)	Group 3 (n = 59)	<i>P</i> value ^a
Preoperative electrocardiogram, No (%)				
Sinus rhythm	71 (61.7)	15 (45.5)	37 (62.7)	.24
Atrial fibrillation	44 (38.3)	16 (48.5)	21 (35.6)	.46
Atrioventricular block	0 (0.0)	1 (3.0)	0 (0.0)	.17
Postoperative electrocardiogram, No (%)				
Sinus rhythm	62 (53.9)	17 (51.5)	28 (47.5)	.71
Atrial fibrillation	45 (39.1)	13 (39.4)	25 (42.4)	.93
Atrioventricular block	5 (4.3)	1 (3.0)	3 (5.1)	.99

TABLE II. Preoperative and Postoperative Rhythms

Mortality

Within the full cohort, 13 patients died. Notably, no statistically significant differences were observed in mortality rates among the groups (P = .42).

Discussion

Presently, mitral valve operations are a routine occurrence worldwide,² with conventional direct left atriotomy being the prevailing incision of choice. Alternative approaches, however, such as superior septal and transseptal left atriotomies, have been developed. Regrettably, these alternative techniques are underused, potentially because of complications reported in previous studies, particularly involving postoperative rhythm disturbances that require permanent pacemaker implantation.

Notably, disparities in baseline parameters were observed, particularly in age. Patients undergoing transseptal atriotomy tended to be younger than patients in the other groups. This divergence in age may influence interpretations of perioperative and postoperative outcomes, given that younger patients typically exhibit fewer comorbidities and tend to recover more swiftly postoperatively.

Observations revealed a preference for using conventional direct left atriotomy in isolated mitral valve operations. Conversely, transseptal left atriotomy emerged as advantageous for mitral valve operations coupled with tricuspid valve interventions,³ enabling enhanced exposure and maneuverability for both valves compared with conventional direct left atriotomy.

Within the superior septal incision group, a higher proportion of patients underwent emergency procedures, typically indicated in cases of infectious endocarditis, papillary muscle rupture, or trauma.^{4,5} This trend elucidates the increased prevalence of endocarditis within the superior septal incision group compared with the other groups. The superior septal atriotomy's capacity to offer superior exposure of the mitral valve over the other atriotomies⁶ contributes to this divergence. Notably, these differences may extended the duration of both ICU and hospital stays observed within this group.

Anatomically, the conventional direct left atriotomy involves a single incision, whereas transseptal and superior septal left atriotomies entail the junction of 2 incisions. The necessity for additional time in opening and closing 2 incisions as opposed to 1 becomes evident, leading to the requirement of less aortic clamping time and CPB time in the case of conventional direct left atriotomy. Moreover, transseptal and superior septal left atriotomies involve incisions extending toward the dome of the left atrium,⁷ an inherently fragile area, necessitating more time and delicacy during the procedure.

Interestingly, no discernible differences were observed among the 3 incision types with respect to postoperative complications, including pulmonary complications, postoperative infections, cardiogenic shock, cerebral lesions, and bleeding. These findings align consistently with the results of other studies.^{8,9}

The literature includes extensive discussions of the impacts of 3 distinct left atrial access incisions on postoperative arrhythmic complications.¹⁰⁻¹⁴ Masuda et al¹⁵ noted in 1996 that although the superior septal incision offers excellent mitral valve exposure, its location poses a risk of damaging the sinus node artery, potentially leading to a higher incidence of arrhythmias than conventional left atriotomy. Contrasting findings were reported by Aydin et al,¹⁶ however, indicating that the superior septal approach did not cause severe or fatal adverse effects on sinus node function compared with conventional direct left atriotomy. Though not statistically significant, the findings of the present study suggest a trend toward postoperative permanent pacemaker implant when using the superior septal left atriotomy, but numerous contributing factors, such as the type and number of associated procedures performed during mitral valve surgery, surgeon experience, and the quality of cardiac tissue being dissected, must be considered.

The maze procedure has been associated with postoperative permanent pacemaker implantation,¹⁷ attributed to factors such as sick sinus syndrome, extensive dissection, and damage to atrial conduction tissues. Similarly, tricuspid valve surgeries may induce postoperative heart rhythm disturbances, potentially necessitating permanent pacemaker implantation.¹⁸ Considering these factors, an exclusion analysis was performed that revealed no statistically significant differences among the 3 atriotomies in terms of postoperative permanent pacemaker implantation.

Turkyilmaz and Kavala¹⁹ highlighted that patients undergoing superior septal left atriotomy exhibited prolonged stays in the ICU and longer total hospital stays, a trend also observed in the present study. It is crucial, however, to consider the impact of infectious endocarditis on these observations.

Infectious endocarditis often induces a systemic inflammatory response syndrome, necessitating increased administration of vasoconstrictive medications. Patients with endocarditis tend to be more medically fragile than those undergoing elective surgeries. Typically, endocarditis cases require intravenous antibiotic therapy lasting 4 to 6 weeks^{20,21} to prevent secondary complications. Therefore, the extended hospitalization times may be more intricately associated with the pathology and the emergent nature of the surgical intervention rather than solely attributable to the choice of incision.

Study Limitations

Given the retrospective nature of this study, the retrieval and management of follow-up and other patient data pose inherent challenges compared with a prospective study design. A notable complexity in this study pertains to the relatively small sample sizes of groups 2 and 3, comprising 33 and 59 patients, respectively. The interpretation of various parameters became intricate because of these smaller sample volumes.

To address limitations in sample size, all patients who underwent mitral valve surgery within the study institution were included, encompassing those with associated procedures during surgery. This approach aimed to augment the sample pool, although it introduced complexities in data analysis and interpretation.

Conclusion

This study underscores the safety of performing mitral valve operations employing these 3 distinct left atrial incisions. Notably, no statistically significant differences were detected concerning postoperative rhythm disturbances and permanent pacemaker implantation, suggesting that the superior septal left atriotomy, with careful consideration of the risk to the sinus node artery, can safely be used.

It is crucial to acknowledge the limitation the relatively small sample sizes in the study groups pose, however, because sample size may affect result interpretation. Future studies incorporating larger sample sizes could provide enhanced statistical power, validating and further substantiating these conclusions.

Article Information

Published: 31 January 2024

Open Access: © 2024 The Authors. Published by The Texas Heart Institute[®]. This is an Open Access article under the terms of the Creative Commons Attribution-NonCommercial License (CC BY-NC, https://creativecommons.org/licenses/by-nc/4.0/), which permits use and distribution in any medium, provided the original work is properly cited, and the use is noncommercial.

Author Contributions: Estelle Démoulin contributed to the acquisition of data and drafting of the manuscript. Mustafa Cikirikcioglu and Estelle Démoulin contributed to the concept

and design and drafting of the manuscript. Dionysios Adamopoulos and Estelle Démoulin contributed to the analysis and interpretation of data and statistical analysis. Tornike Sologashvili, Mathieu van Steenberghe, Jalal Jolou, Haran Burri, and Christoph Huber contributed to the concept and design and drafting of the manuscript.

Conflict of Interest/Disclosure: None.

Funding/Support: None.

Meeting Presentation: Presented at International Heart Valve Congress 2023 by the World Society of Cardiovascular and Thoracic Surgeons and the Royal College of Surgeons of Edinburgh; February 10-12, 2023; Edinburgh, United Kingdom.

References

- Cohn LH. Fifty years of open-heart surgery. *Circulation*. 2003;107(17):2168-2170. doi:10.1161/01. CIR.0000071746.50876.E2
- Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol.* 2011;8(3):162-172. doi:10.1038/ nrcardio.2010.202
- Nienaber JJ, Glower DD. Minitransseptal versus left atrial approach to the mitral valve: a comparison of outcomes. *Ann Thorac Surg.* 2006;82(3):834-839; discussion 839. doi:10.1016/j.athoracsur.2006.04.014
- Marchetta S. Therapeutic news in infective endocarditis. Article in French. *Rev Med Suisse*. 2016;12(527):1358-1361.
- Carballo S, Rossel A, Carballo. Diagnostic et prise en charge précoce des endocardites infectieuses. *Rev Med Suisse*. 2012;8(358):1966-1971.
- Alfieri O, Sandrelli L, Pardini A, et al. Optimal exposure of the mitral valve through an extended vertical transeptal approach. *Eur J Cardiothorac Surg.* 1991;5(6):294-298; discussion 299. doi:10.1016/1010-7940(91)90038-1
- Kumar N, Saad E, Prabhakar G, De Vol E, Duran CM. Extended transseptal versus conventional left atriotomy: early postoperative study. *Ann Thorac Surg.* 1995;60(2):426-430. doi:10.1016/0003-4975(95)00449-u
- Rezahosseini O, Rezaei M, Ahmadi Tafti SH, et al. Transseptal approach versus left atrial approach to mitral valve: a propensity score matching study. *J Tehran Heart Cent.* 2015;10(4):188-193.

- 9. Hartz RS, Kanady KE, LoCicero 3rd J, Sanders JH, DePinto DJ. Oblique transseptal left atriotomy for optimal mitral exposure. *J Thorac Cardiovasc Surg.* 1992;103(2):282-286.
- Boulemden A, Nadarajah D, Szafranek A, Richens D. Atrial approaches to the mitral valve: is there a difference in postoperative rhythm disturbance and permanent pacemaker implantation? *Interact Cardiovasc Thorac Surg.* 2018;27(4):536-542.
- Lukac P, Hjortdal VE, Pedersen AK, Mortensen PT, Jensen HK, Hansen PS. Superior transseptal approach to mitral valve is associated with a higher need for pacemaker implantation than the left atrial approach. *Ann Thorac Surg.* 2007;83(1):77-82. doi:10.1016/j.athoracsur.2006.08.034
- Utley JR, Leyland SA, Nguyenduy T. Comparison of outcomes with three atrial incisions for mitral valve operations. Right lateral, superior septal, and transseptal. J Thorac Cardiovasc Surg. 1995;109(3):582-587. doi:10.1016/ S0022-5223(95)70292-X
- Misawa Y, Fuse K, Kawahito K, Saito T, Konishi H. Conduction disturbances after superior septal approach for mitral valve repair. *Ann Thorac Surg.* 1999;68(4):1262-1264;discussion 1264-1265. doi:10.1016/ s0003-4975(99)00666-9
- Izzat MB, Aljasem H, Alsharabi M, Hafez A. Comparison of safety and outcomes with two approaches to the mitral valve. *J Card Surg.* 2020;35(7):1458-1463. doi:10.1111/jocs.14603
- Masuda M, Tominaga R, Kawachi Y, et al. Postoperative cardiac rhythms with superior-septal approach and lateral approach to the mitral valve. *Ann Thorac Surg.* 1996;62(4):1118-1122.
- Aydin E, Arslan A, Ozkokeli M. Comparison of superior septal approach with left atriotomy in mitral valve surgery. *Rev Bras Cir Cardiovasc.* 2014;29(3):367-373. doi:10.5935/1678-9741.20140045
- Cox JL, Ad N, Churyla A, et al. The maze procedure and postoperative pacemakers. *Ann Thorac Surg.* 2018;106(5):1561-1569. doi:10.1016/j.athoracsur.2018.05.013
- 18. Mahboobi SK, Ahmed AA. *Tricuspid valve repair*. In: StatPearls. StatPearls Publishing; 2022.
- Turkyilmaz S, Kavala AA. Comparison of left atriotomy and superior transseptal approaches in mitral valve surgery. *Heart Surg Forum.* 2018;21(4):E318-E21. doi:10.1532/hsf.1997
- 20. Pettersson GB. Surgical treatment of endocarditis: current status. *Tex Heart Inst J.* 2011;38(6):667-668.
- Kilic A. Infective endocarditis: a multidisciplinary approach. 2022. Accessed June 13, 2022. https://www.clinicalkey. com/#!/browse/book/3-s2.0-C20190020559