Bölüm 2

KILAVUZLAR EŞLİĞİNDE EDİNSEL AORT DARLIĞI VE CERRAHİ TEDAVİSİ

Necmettin YAKUT[1]

GİRİŞ

Aortik kapak, sol ventrikül çıkım yolu (LVOT) ile aort arasında yer alan semilunar bir kapaktır. Sistemik kalp debisinin sağlanması için bu kapağın normal yapıda ve fonksiyonel olması önemlidir. Kapakta meydana gelebilecek patolojik değişikliklerin iyi anlaşılabilmesi ve düzeltilebilmesi için anatomik ve fizyolojik özelliklerinin iyi bilinmesi gerekmektedir.

TARİHÇE

Aort kapağına cerrahi yaklaşım ilk olarak 1914 yılında Tuffier tarafından aort darlığı olan bir hastaya aortik kommisürotomi yapılması ile başlamıştır (1,2). Deneysel aortik valvotomi çalışması ilk defa 1947'de, Charleston'daki Güney Carolina Üniversitesi'nden Smithy ve Parker tarafından bildirildi (3). 1950'lerin başlarında Bailey ve arkadaşları bir mekanik dilatör yardımı ile retrograd olarak asendan aortadan, aort kapağına ulaşarak kapak kommisürlerindeki yapışıklıkları giderdiler (1, 4, 5). Bu yöntem ile bazı hastalarda orta derecede bir başarı elde ettiler. Aort kapak hastalıklarında etkili cerrahi tedavi, Gibbon tarafından 1953 yılında kalp-akciğer makinesinin geliştirilmesi ve kardiyopulmoner baypas(CPB)'ın uygulanabilmesi ile başlamıştır.

1960'da Kirklin ve Mankin, 1963'de ise Scannell ve arkadaşları kardiopulmoner baypası kullanarak ilk aortik valvotomileri gerçekleştirmişlerdir (6,7). Bu aşamada sadece valvotomi ve dekalsikasyon yapılabiliyordu.

1960'da Bahson ve arkadaşları ile1961'de bağımsız olarak Hufnagel ve Conrad tek leafletli protezi geliştirdikten sonra aort kapağın parsiyel replasmanını yaptılar. İlk total aortik valv replasmanı (AVR) McGoon tarafından 1961'de Mayo klinikte politetrafloroetilenden (PTFE) kapak geliştirildikten sonra uygulanmıştır (1).

[1] Operatör Doktor, İzmir Özel Akut Kalp Damar Hastanesi, info@akutkalpdamar.com

görülür. TAVI işleminden sonra hastaların yaklaşık üçte birinde yeni başlangıçlı atriyal fibrilasyon gelişebilir. İşlemden sonraki ilk 24 saatte ortaya çıkan serebrovasküler komplikasyonların bu yeni başlangıçlı atriyal fibrilasyon ile ilişkili olduğu düşünülmektedir. Embolik materyalin kaynağı genellikle doğal aort kapak yaprakçıkları veya aort duvarıdır.

7-Kanama: TAVI uygulanan hastalarda perikard aralığına kanama nedeniyle oluşan kardiyak tamponad yaklaşık %3-4 oranında görülür ve yüksek ölüm oranına (%24) sahiptir (93).

8- Kalp İleti sistemi Hasarı: TAVI sonrası ileti sitemi hasarı gelişimi %5,7-42,5 arasındadır. Uzamış atriyoventriküler iletim zamanı, atriyoventriküler blok, sol dal bloğu ve kalıcı pacemaker ihtiyacı TAVI`ye bağlı ileti sistemi hasarları olarak sayılabilir (94).

9-Akut Renal Hasar: Akut renal hasar gelişmesi oranı %22 civarındadır (95).

10-Ölüm: Ölüm oranı %5-10 arasında değişmektedir. TAVI işleminden sonraki ilk 48 saatte ölüm nedeni çoğunlukla (% 75) kalp (yetmezlik, tamponad ve aritmi) kaynaklıdır. 48 saatten sonra kalp dışı nedenler (enfeksiyon, sepsis ve inme) % 69 oranında en sık karşılaşılan ölüm nedenleridir (96).

KAYNAKÇA

1. İlhan G, Depboylu BC, Yazman S. Aort Darlığı. Kaygın MA, Erkut B. Kalp Damar Cerrahisinde Güncel Yaklaşımlar. 2019; 335-380. Akademisyen Kitabevi.
2. Kıraali K, Tuncer A. Aort Darlığı. Paç M, Akçevin A, Aykut Aka S, Buket S, Sarıoğlu T. Kalp ve Damar Cerrahisi 2013; 627-664 Ankara Medikal Network Nobel Kitabevi.
3. Smithy HG, Parker EF: Experimental aortic valvulotomy, preliminary report. Surg Gynecol Obstet 1947;34: 625-33
4. Bailey CP, Glover RP, O'Neill TJE, Redondo-Ramirez HR: Experience with the experimental surgical relief of aortic stenosis: A preliminary report. J Thorac Surg 1952;2: 516-41
5. Bailey CP, Redondo-Ramirez HR, Larzelere HB: Surgical treatment of aortic stenosis. JAMA 1952;150:1647-52
6. Hurley PJ, Lowe JB, Barratt-Boyes BG. Depridement valvotomy for aortic stenosis in adults. A follow up of 76 patients. Thorax 1967;22: 314-9
7. Kirklin JW, Mankin HT: Open operation in the treatment of calcific aortic stenosis. Circulation 1960;21: 578-86
8. Starr A, Edwards M, Mccord CW, Griswold HE: Aortic replacement: Clinical experience with a semirigid ball-valve prothesis. Circulation 1971;44: 368.
9. Ross DN: Homograft replacement of the aortic valve. Lancet 1962. 8;2: 487.
10. Donaldson RM, Ross DM: Homograft aortic root replacement for complicated prosthetic valve endocarditis. Circulation 1984;7(supplI):I-178-81
11. Ross DN, Martelli V, Wain WH: Allograft and autograft valves used for aortic valve replacement. In MI Ionescu (ed): Tissue Heart Valves. London: Butterworth,1979;27(1):31-8
12. Ross DN: Replacement of aortic and mitral valve with a pulmonary autograft. Lancet 1967;2: 956-8
13. Binet JP, Duran CG, Carpentier A, Langlois J: Heterologous aortic valve transplantation. Lancet 1965;2 (7425):1275.

14. Carpentier A, Lemaigre G, Robert L, Carpentier S, Dubost C: Biological factors affecting long-term results of valvular heterografts. J Thorac Cardiovasc Surg 1969;58: 467-83
15. Nicholas T, Kouchoukos, Eugene H.Blackstone, Frank L.Hanley, et al. Kiklin/Barrat-Boyes Cardiac surgery (2013). Philadelphia Saunders, Elsevier Inc.
16. Moore KL, Persaud TVN editors. The cardiovascular system: In: The developing human : Clinically oriented embryology. 5th ed. Philadephia, W.B. Saunders Company, 1993:403-353
17. Koçarslan A, Eroğlu E, Acıpayam M. Aort kapağı anatomisi. Emiroğulları ÖN, editör. Aort Kapak Hastalıkları ve Tedavisi. 1. Baskı. Ankara: Türkiye Klinikleri; 2019. p.1-4.
18. Carpentier A, Adams DH, Filsoufi F. Aortic vale reconstruction. In: Carpentier's reconstructive valve surgery. 1st ed. Missouri: Saunders,Elsevier; 2010. p.209-27.
19. N. Bozbuğa, A. Ozturk , F. Nurozler ve ark. Aort kapak ve sol ventrikul cıkım yolunun morfometrik ozelliklerinin incelenmesinde matematiksel cozumlemenin kullanılması. Turk Goğus Kalp Damar Cer. Derg. 2000;8;682-686
20. Hinton RB, Yutzey KE. Heart valve structure and function in development and disease. Annu Rev Physiol. 2011;73: 29-46.
21. Hanna MF, Malguria N, Saboo SS, et al. Crosssectional imaging of sinus of Valsalva aneurysms: lessons learned. Diagn Interv Radiol. 2017;23(5):339-46.
22. Berdajs D, Lajos P, Turina M. The anatomy of the aortic root, Cardiovasc Surg. 2002;10(4): 320-7.
23. Sutton JP 3rd, Ho SY, Anderson RH. The forgetten interleaflet triangles: A review of the surgical anatomy of the aortic valve. Ann Thorac Surg. 1995;59(2):419-27.
24. Gnyaneshwar R, Kumar RK, Balakrishnan KR. Dynamic analysis of the aortic valve using afinite element model. Ann Thorac Surg. 2002;73:1122-1129
25. Vahanian A, Alfieri O, Andreotti F, et al. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (**ESC**) and the European Association for Cardio-Thoracic Surgery (EACTS). [Guidelines on the management of valvular heart disease (version **2012**). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (**ESC**) and the European Association for Cardio-Thoracic Surgery (EACTS)]. G Ital Cardiol (Rome). 2013 Mar;14(3):167-214. doi: 10.1714/1234.13659
26. Baumgartner H. The 2017 **ESC**/EACTS guidelines on the management of valvular heart disease: What is new and what has changed compared to the **2012** guidelines? Wien Klin Wochenschr. 2018 Mar;130(5-6):168-171. doi: 10.1007/s00508-017-1297-5.
27. Osnabrugge RL, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013; 62: 1002-12.
28. Elçik D, Tunçay A, İnanç MT, et al. Aort darlığı ve tedavisi. Emiroğulları ÖN, editör. Aort Kapak Hastalıkları ve Tedavisi. 1. Baskı. Ankara: Türkiye Klinikleri; 2019. p.5-10.
29. Huntley GD, Thaden JJ, Alsidawi S, et al. Comparative study of bicuspid vs. tricuspid aortic valve stenosis. Eur Heart J Cardiovasc Imaging. 2018;19(1):3-8.
30. Owens DS, Katz R, Takasu J, et al. Incidence and progression of aortic valve calcium in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Cardiol. 2010;105(5):701-8.
31. Towler DA. Molecular and cellular aspects of calcific aortic valve disease. Circ Res. 2013;113(2):198-208.
32. Rosseb AB, Pedersen TR, Boman K, et al; SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008;359(13):1343-56.
33. Bonow RO, Carabello BA, de Leon AC Jr, et al. Guidelines for the management of patients with valvular heart disease: Executive summary. A report of the American Collage of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committe on Management of Patients With Valvular Heart Disease). Circulation. 1998;98(18):1949-84.
34. Tracy GP, Proctor MS, Hizny CS. Reversibility of pulmonary artery hypertension in aortic stenosis after aortic valve replacement. Ann Thorac Surg. 1990;50(1):89-93

35. Blumberg FC, Pfeifer M, Holmer SR, et al. Transgastric Doppler echocardiographic assessment of the severity of aortic stenosis using multiplane transesophageal echocardiography. Am JCardiol 1997; 79(9):1273-1275.
36. Braunwald E, Valvular heart disease. Braunwald E, Zipes DP, Libby P. (eds). Heart Disease. A Textbook of Cardiovascular Medicine Philadephia, W.B. Saunders, 2001 P;1643-1722
37. Otto CM. Calcification of bicuspid aortic valves. Heart 2002;88: 321-2
38. Carabello BA. Clinical practice. Aortic stenosis. N Eng J Med. 2002;28: 346(9):677-82
39. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611-617.
40. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;111: 3290-3295.
41. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. Circulation 2010;121:151-156
42. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation. 2005; 111: 920-5.
43. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597-607.
44. Eleid MF, Goel K, Murad MH, et al. Metaanalysis of the prognostic impact of stroke volume, gradient, and ejection fraction after transcatheter aortic valve implantation. Am J Cardiol. 2015;116(6):989-94.
45. Otto CM. Aortic stenosis. Clinical evaluation and optimal timing surgery. Cardiol Clin.1998; 16(3):353-73
46. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation. 2005; 111(24):3290-5.
47. Bergler-Klein J, Klaar U, Heger M et al. Natriuretic peptides predict symptom-free survival andpostoperative outcome in severe aortic stenosis. Circulation, 2004;109:2302-8.
48. Vincentelli A, Susen S, Le Tourneau T et al. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med, 2003;349:343-9.
49. Otto CM . Valvular stenosis: diagnosis, quantitation, and clinical approach. In Otto CM(ed). Textbook of Clinical Echocardiography. Philadephia, W.B. Saunders. 2000,pp 229-238
50. Nishimura RA, Otto CM, Bonow RO, et al: 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the ACC/AHA Task Force on Practice Guidelines. J Am Coll Cardiol, doi: 10. 1016/j.jacc. 2014.02.536.
51. Vahanian A, Baumgartner H, Bax J, et al: Guidelines on the management of valvular heart disease. Eur Heart J. 2007;28:230-68.
52. Elçik D, Tunçay A, Doğan A. Aort kapak hastalıklarının ekokardiyografi ile değerlendirilmesi. Emiroğulları ÖN, editör. Aort Kapak Hastalıkları ve Tedavisi. 1. Baskı. Ankara: Türkiye Klinikleri; 2019. p.24-8.
53. Monin JL, Quere JP, Monchi M et al. Low-gradient aorticstenosis, operative risk stratification and predictors for long-term outcome: A multicenter study using dobutamine stres hemodynamics. Ciculation, 2003;108:319-24.
54. Lancellotti P, Pellikka PA, Budts W, et al. Theclinical use of stres echocardiography in nonischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging. 2016;17(11): 1191-229
55. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. Eur Heart J, 2005;26:1309-13.
56. Melina G, Scott MJ, Cunanan CM, Rubens MB, Yacoub MH: In-vitro verification of the electron beam tomography method for measurement of heart valve calcification. J Heart Valve Dis 2002; 11(3):402-407; discussion408.

57. Myerson SG. Heart valve disease: investigation by cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2012; 14:7.
58. Cawley PJ, Maki JH, Otto CM: Cardiovascular magnetic resonance imaging for valvular heart disease: technique and validation. Circulation 2009; 119(3):468-478.
59. Cribier A, Eltchaninoff H, Tron C, et al. Early experience with percutaneous transcathater implantation of heart valve prosthesis for the treatment of end – stage inoperable patients with calcific aortic stenosis. J Am Coll Cardiol. 2004;43(4):698-703
60. Bonow RO, Carabello BA, Chatterjee K et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol, 2008;52:e1-142
61. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, et al: Predictors of outcome in severe, asymptomatic aortic stenosis. NEJM 2000; 343(9):611-617.
62. Pai RG, Kapoor N, Bansal RC, Varadarajan P: Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. Ann Thorac Surg 2006; 82(6):2116-2122
63. Varadarajan P, Kapoor N, Bansal RC, et al: Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: results from a cohort of 277 patients aged > or = 80 years. Eur JCardiothoracic Surg 2006; 30(5):722- 727.
64. Mihaljevic T, Nowicki ER, Rajeswaran J, et al: Survival after valve replacement for aortic stenosis: implications for decision making. J Thorac Cardiovasc Surg 2008; 135(6):1270-1278; discussion 1278-1279.
65. Gokhan Ilhan, Sahin Bozok, Berkan Ozpak, Hakan Kara, et al: Anatomical and functional changes after aortic valve replacement with different sizes of mechanical valves. Cardiovascular Journal of Africa 2018,Volume 29, No 6;338-343.
66. Taniguchi T, Morimoto T, Shiomi H, et al. Initial Surgical Versus Conservative Strategies in Patients With Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2015;66: 2827-38.
67. Kalavrouziotis D, Li D, Buth KJ, et al. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is not appropriate for withholding surgery in high-risk patients with aortic stenosis: a retrospective cohort study. J Cardiothorac Surg. 2009;4: 32.
68. Maréchaux S, Hachicha Z, Bellouin A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. Eur Heart J. 2010;31: 1390-7.
69. Cimadevilla C, Cueff C, Hekimian G, et al. Prognostic value of B type natriuretic peptide in elderly patients with aortic valve stenosis:the COFRASA-GENERAC study. Heart. 2013;99:461-7.
70. Brown J, O'Brien SM, Wu C, et al. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types and outcomes in the society of thoracic surgeons national database. J Thorac Cardiovasc Surg. 2009;137:82-90.
71. Borger MA, Moustafine V, Conradi L, et al. A randomized multicenter trial of minimally invasive rapid deployment versus conventional full sternotomy aortic valve replacement. Ann Thorac Surg 2015;99: 17-25.
72. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol. 2012;60: 548-58.
73. Giordana F, D'Ascenzo F, Nijhoff F, et al. Meta-analysis of predictors of allcause mortality after transcatheter aortic valve implantation. Am J Cardiol. 2014;114:1447-55.
74. Folliguet TA, Laborde F, Zannis K, et al. Sutureless Perceval aortic valve replacement: results of two European centers. Ann Thorac Surg. 2012; 93: 1483-8.
75. Martens S, Ploss A, Sirat S, et al. Sutureless aortic valve replacement with the 3f Enable aortic bioprosthesis. Ann Thorac Surg. 2009;87: 1914-7.

76. Magovern GJ, Cromie HW. Sutureless prosthetic heart valves. J Thorac Cardiovasc Surg. 1963;46: 726-36.
77. Eroğlu E, Koçarslan A, Acıpayam M, Yasım A. Aort kapak hastalıkları tedavisinde yeni yöntemler: Sütürsüz kapaklar. Emiroğulları ÖN, editör. Aort Kapak Hastalıkları ve Tedavisi. 1. Baskı. Ankara: Türkiye Klinikleri; 2019. p.47-52.
78. Eusanio M, Phan K. Sutureless aortic valve replacement.Ann Cardiothorac Surg 2015;4(2):123-130.
79. Chalmers J, Pullan M, Mediratta N, et al. A need for speed? Bypass time and outcomes after isolated aortic valve replacement surgery. Interact Cardiovasc Thorac Surg 2014;19: 21-6.
80. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol 2013;61: 1585-95.
81. Cribier A. Arch Cardiovasc Dis. Development of transcatheter aortic valve implantation (TAVI): a 20-year odyssey. 2012;105(3):146-52.
82. Smith CR, Leon MB, Mack MJ, et al. PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
83. Kalay N, Elçik D, Tunçay A. Aort kapak hastalıkları tedavisinde yeni yöntemler: TAVİ. Emiroğulları ÖN, editör. Aort Kapak Hastalıkları ve Tedavisi. 1. Baskı. Ankara: Türkiye Klinikleri;2019. p.53-6.
84. Depboylu BC, Yazman S, Harmandar B. Complications of transcatheter aortic valve replacement and rescue attempts. Vessel Plus 2018;2: 26.
85. Baumgartner H, Falk V, Bax JJ, et al. ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease Eur Heart J. 2017;38(36):2739-91.
86. Barbanti M, Yang TH, Rodes Cabau J, et al. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. Circulation 2013;128:244-53.
87. Khatri PJ, Webb JG, Rodes-Cabau J,et al. Adverse effects associated with transcatheter aortic valve implantation: a meta-analysis of contemporary studies. Ann Intern Med 2013;158: 35-46.
88. Ryś M, Hryniewiecki T, Michałowska I, et al. Quantitative estimation of aortic valve calcification in multislice computed tomography in predicting the development of paravalvular leaks following transcatheter aortic valve replacement. Postepy Kardiol Interwencyjnej 2018;14: 85-9.
89. Paradis JM, Del Trigo M, Puri R, et al. Transcatheter valve-in-valve and valve-in-ring for treating aortic and mitral surgical prosthetic dysfunction. J Am Coll Cardiol 2015; 66: 2019-37.
90. Ribeiro HB, Nombela-Franco L, Urena M,et al. Coronary obstruction following transcatheter aortic valve implantation: a systematic review. JACC Cardiovasc Interv 2013;6: 452-61.
91. Genereux P, Head SJ, Van Mieghem NM,et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol 2012;59:2317-26.
92. Stortecky S, Windecker S, Pilgrim T, et al. Cerebrovascular accidents complicating transcatheter aortic valve implantation: frequency, timing and impact on outcomes. EuroIntervention 2012;8: 62-70.
93. Van Mieghem NM, Schipper ME, Ladich E, et al. Histopathology of embolic debris captured during transcatheter aortic valve replacement. Circulation 2013;128:e478-9.
94. Rezq A, Basavarajaiah S, Latib A, et al. Incidence, management, and outcomes of cardiac tamponade during transcatheter aortic valve implantation: a single-center study. JACC Cardiovasc Interv 2012;5: 1264-72
95. Nuis RJ, Van Mieghem NM, Schultz CJ, et al. Timing and potential mechanisms of new conduction abnormalities during the implantation of the Medtronic CoreValve System in patients with aortic stenosis. Eur Heart J 2011;32: 2067-74.
96. Takagi H, Niwa M, Mizuno Y, et al. All-Literature Investigation of Cardiovascular Evidence Group. Incidence, predictors, and prognosis of acute kidney injury after transcatheter aortic valve implantation: a summary of contemporary studias using Valve Academic Research Consortium definations. Int J Cardiol 2013;168:1631-5.