Efficacy and Safety of External Extracorporeal Counterpulsation in Heart Failure with Preserved Ejection Fraction

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Abstract

This review study explores the therapeutic potential of External Extracorporeal Counterpulsation (EECP) in the context of Heart Failure with Preserved Ejection Fraction (HFpEF). Drawing from various studies, the analysis delves into the mechanisms of action underlying EECP, emphasizing its impact on exercise capacity, symptomatic relief, and different cardiovascular parameters. The research suggests that EECP, with its multifaceted effects on endothelial function, oxidative stress reduction, and promotion of angiogenesis, holds promise as a tailored intervention for HFpEF. Despite promising outcomes, the review acknowledges limitations, such as the need for standardized protocols and further large-scale trials. Looking ahead, the future direction of research is envisioned to refine patient selection criteria, optimize treatment regimens, and assess the long-term implications of EECP in HFpEF management. This abstract encapsulates the evolving landscape of cardiovascular therapeutics, positioning EECP as a noteworthy modality deserving continued exploration for its efficacy, safety, and potential integration into the holistic care of HFpEF patients.

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is a cardiovascular disorder that presents a significant burden on healthcare systems and the lives of affected individuals [1]. HFpEF is characterized by the heart's inability to relax and fill during the diastolic phase effectively, which impairs its ability to pump blood efficiently [2]. This results in reduced cardiac output and a range of symptoms, such as shortness of breath, fatigue, and fluid retention [3]. Despite its increasing prevalence, effective treatments for HFpEF have remained elusive, and managing the condition remains a considerable challenge for healthcare providers [4]. In recent years, medical researchers and practitioners have been exploring alternative therapeutic options for HFpEF, given the limited success of traditional heart failure treatments. One such approach that has gained attention is external extracorporeal counterpulsation (EECP). EECP is a non-invasive and hemodynamic therapy that uses inflatable cuffs placed around the patient's lower extremities, which are timed to inflate and deflate in coordination with the cardiac cycle [5]. This synchronized inflation and deflation creates a pulsatile effect that augments diastolic blood flow, reduces cardiac afterload (the resistance the heart must overcome to pump blood), and enhances coronary perfusion (blood supply to the heart muscle)[5]. While EECP has shown promise in improving symptoms and quality of life in patients with heart failure with reduced ejection fraction, its application and effectiveness in the context of HFpEF require further investigation. HFpEF presents distinct challenges due to its unique pathophysiology, primarily related to diastolic dysfunction rather than systolic dysfunction [2]. Therefore, determining whether EECP can provide meaningful benefits to HFpEF patients is a subject of ongoing research and clinical debate. This research seeks to comprehensively assess the efficacy and safety of EECP in managing HFpEF. The approach involves a thorough review of existing literature, clinical trials, and emerging evidence to evaluate the potential advantages and drawbacks of EECP in the context of HFpEF. Given its distinct pathophysiological features and therapeutic needs, the overarching goal is to shed light on whether EECP can be considered a viable therapeutic option for patients suffering from HFpEF. Understanding the potential benefits and risks of EECP in the context of HFpEF is crucial for guiding clinical decision-making and improving the management of this challenging condition, ultimately improving the quality of life for those affected.

External Extracorporeal Counterpulsation (EECP)

EECP emerges as a non-invasive therapeutic breakthrough with a rich historical background and substantial efficacy in cardiovascular management. Originating in the late 1960s with a primary focus on alleviating angina, EECP has evolved significantly, expanding its application to diverse cardiovascular conditions [6]. The contemporary use of EECP in heart failure is rooted in its historical development, conceived as a strategic approach to augment coronary blood flow while

diminishing myocardial oxygen demand [7]. The pivotal mechanisms dictating EECP's cardiovascular benefits are integral to its therapeutic prowess.

The standard EECP course comprises 35 one-hour sessions scheduled each week from Monday to Friday[7]. Alternatively, patients may choose to undergo two sessions per day if tolerated. The therapy duration can be extended for those showing delayed symptom improvement, with additional treatment hours considered based on individual treatment objectives [7]. Progress measurement varies, with a reduction in angina symptoms as a marker for those initially presenting with angina [8]. Exclusion criteria, as per Vasomedical protocol, include arrhythmias interfering with machine triggering, bleeding diathesis, active thrombophlebitis, severe lower extremity vaso-occlusive disease, documented aortic aneurysm requiring surgical repair, and pregnancy [7][9]. Precautions involve conditions like decompensated heart failure, aortic insufficiency, severe mitral or aortic stenosis, uncontrolled hypertension, and heart rates exceeding 120 beats per minute [10]. Notably, hypertension and elevated heart rates should be managed before initiation, and heart failure patients should achieve stability before treatment. EECP is generally well-tolerated, with typical equipment-related side effects, including leg and back pain, skin abrasion, bruising, blistering, edema, and paresthesias [10]. Beneficial effects include reduced myocardial oxygen demand, increased venous return and cardiac output, improved endothelial function, prolonged time to exercise-induced ST depression on 12-lead electrocardiogram, and improvement or resolution of myocardial perfusion defects [7][10][11]. According to the International EECP Patient Registry (IEPR), in 2000, EECP demonstrated a high level of safety, with minimal adverse events reported among the treated patients [7].

The non-invasive nature of EECP further enhances its appeal, positioning it as an attractive adjunctive therapy for heart failure patients and establishing its relevance in the cardiovascular care continuum. This thorough comprehension of EECP's historical evolution, intricate mechanisms of action, and versatile applications in heart failure underscores its paramount significance as a therapeutic modality within the complex landscape of cardiovascular medicine.

Rationale for Investigating EECP in HFpEF

The rationale for investigating EECP in HFpEF stems from a multifaceted perspective. Critical differences between HFpEF and heart failure with reduced ejection fraction (HFrEF) are pivotal in guiding this exploration. HFpEF is characterized by impaired diastolic function, distinguishing it from HFrEF, which primarily involves systolic dysfunction [12]. Recognizing these unique pathophysiological features underscores the need for therapeutic interventions tailored to the specific challenges posed by HFpEF. EECP, with its ability to augment diastolic blood flow, reduce cardiac afterload, and improve coronary perfusion, holds the intrinsic potential to address the distinctive challenges presented by HFpEF [13]. The non-invasive nature of EECP aligns with the nuanced characteristics of HFpEF, offering a potential avenue for therapeutic benefit [7]. A notable research gap in well-established therapeutic options for HFpEF further accentuates the significance of exploring alternative treatments. Conventional heart failure medications, primarily designed for systolic dysfunction, often demonstrate limited efficacy in HFpEF. [2] Thus, the investigation of EECP emerges as a crucial endeavor to fill this therapeutic void, presenting an opportunity to expand and enrich the armamentarium for HFpEF management. This exploration contributes to our evolving understanding of HFpEF and can potentially enhance patient outcomes in a

condition where effective interventions are currently scarce.

External Extracorporeal Counterpulsation Mechanisms of Action in HFpEF

EECP demonstrates multifaceted mechanisms of action in HFpEF[14]. EECP involves three sets of pneumatic cuffs applied to the patient's legs, initiating inflation synchronized with the R wave of the electrocardiogram. This process induces a retrograde flow in the aorta during diastole, augmenting blood flow and enhancing venous return. The resulting decrease in vascular resistance assists with systolic unloading and reduces cardiac workload [7][13]. The therapy's impact on diastolic augmentation and coronary perfusion pressure contributes to its efficacy. EECP's ability to improve endothelial function, increase venous return and cardiac output, and reduce myocardial oxygen demand further underscores its beneficial effects in HFpEF [10].

One key mechanism involves the enhancement of endothelial function. EECP has demonstrated immediate increases in the reactive hyperemia-peripheral arterial tonometry index, indicative of improved peripheral endothelial function [15]. Considering the pivotal role of endothelial dysfunction in HFpEF, these findings suggest that EECP might address a critical aspect of the pathophysiology by promoting better vascular homeostasis. Moreover, the reduction in oxidative stress and pro-inflammatory cytokines observed in EECP-treated patients aligns with mitigating the inflammatory milieu associated with HFpEF [8]. EECP creates a favorable environment by positively influencing neurohormonal regulation, angiogenesis, and endothelial progenitor cell activity [16]. These mechanisms collectively contribute to the potential efficacy of EECP in HFpEF by addressing multiple facets of the complex cardiovascular dysfunction characteristic of the condition.

Diagnosis of HFpEF

In the realm of HFpEF diagnosis, challenges persist due to the heterogeneous nature of the syndrome and the absence of distinct diagnostic markers. Current diagnostic criteria rely on a combination of clinical symptoms, preserved ejection fraction, and evidence of cardiac structural or functional abnormalities [2]. However, ongoing research emphasizes the need to explore novel diagnostic tools to enhance precision in HFpEF diagnosis. Advanced imaging modalities and biomarkers could provide valuable insights into the underlying pathophysiology, allowing for more accurate and timely identification of HFpEF [12]. Given the evolving understanding of HFpEF as a syndrome with diverse etiologies, personalized diagnostic approaches might be essential. Incorporating emerging technologies and refining diagnostic criteria will be crucial for improving the accuracy of HFpEF diagnosis, facilitating early intervention, and enhancing patient outcomes.

Treatment Options for HFpEF

The treatment landscape for HFpEF involves a multifaceted approach, with emerging evidence suggesting a potential role

for EECP. Traditional management strategies for HFpEF focus on controlling comorbidities, optimizing fluid balance, and employing pharmacological interventions [17]. In this context, EECP presents a novel avenue with its unique mechanisms of action. By enhancing peripheral arterial tonometry and promoting reactive hyperemia, EECP improves endothelial function, potentially addressing the underlying vascular abnormalities seen in HFpEF. Additionally, EECP has demonstrated benefits in reducing oxidative stress and inflammation, which are implicated in HFpEF pathophysiology. This non-invasive therapy may serve as an adjunct to conventional treatments, offering a promising option for patients who may not respond adequately to standard pharmacotherapy.

Previous studies have suggested a higher occurrence of heart failure in individuals with impaired left ventricular function, as EECP might elevate venous return and preload, potentially triggering pulmonary edema [18]. In the Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) trial involving 187 participants diagnosed with stable, symptomatic, mild-to-moderate heart failure (with a left ventricular ejection fraction [LVEF] ≤35%) and receiving optimal medical therapy, those undergoing EECP demonstrated a noteworthy improvement in exercise duration, with a 10% increase (from 25% to 35%) compared to the control group [19]. This improvement was observed immediately after treatment and persisted for up to three months, as reflected in the Minnesota Living with Heart Failure score. However, there was no substantial variance in peak oxygen consumption (peak VO2) between the EECP and control groups. A subgroup analysis focusing on individuals aged 65 and above from the PEECH trial displayed a considerably higher response rate in the peak VO2 group (29.7%) compared to the control group (11.4%) at the six-month mark [20].

Further evaluation from the PEECH trial revealed that following EECP therapy, approximately one-third of patients exhibited an improvement of at least one class in the New York Heart Association (NYHA) classification at one week, and this improvement persisted at six months post-therapy. Notably, a smaller percentage of patients in the placebo group reported similar results [20]. Not only did EECP show promise in enhancing exercise capacity and NYHA classification, but it also displayed positive impacts on patients' quality of life. Patients who underwent EECP reported improvements in their quality-of-life assessments at one week and six months post-treatment, and these beneficial outcomes were achieved without significant complications. In a separate study involving 450 patients experiencing refractory angina and left ventricular dysfunction (with an ejection fraction [EF] < 30 ± 8%), EECP was found to significantly reduce emergency room visits by 78% and hospitalizations by 73% over six months [21]. A prospective cohort study revealed noteworthy improvements in several biomarkers after EECP therapy compared to baseline. These improvements included significant enhancements in B-type natriuretic peptide, uric acid levels, free-T3/free-T4 ratio, and mitral annular E velocity [22].

Additionally, EECP therapy demonstrated significant increases in left ventricular ejection fraction (LVEF) and notable reductions in resting heart rate [23]. Moreover, EECP therapy exhibited positive effects in patients with both ischemic and non-ischemic cardiomyopathy, whether it was associated with systolic or diastolic dysfunction [24]. A specific study involving 26 patients diagnosed with heart failure (classified as NYHA class II/III and an average EF of 23%) showed clinical benefits without any significant adverse cardiac effects attributable to EECP therapy [25].

Limitations

Despite the potential therapeutic benefits, External Extracorporeal Counterpulsation (EECP) in the context of Heart Failure with Preserved Ejection Fraction (HFpEF) has certain limitations that merit consideration. One notable constraint is the limited pool of rigorous, large-scale clinical trials explicitly addressing the efficacy of EECP in HFpEF. The existing body of evidence primarily consists of studies exploring EECP in broader cardiovascular contexts, and the extrapolation of findings to HFpEF requires caution. Moreover, the optimal patient selection criteria for EECP in HFpEF still need to be defined, making it challenging to identify individuals who would benefit most. The long-term effects and durability of EECP in HFpEF management also necessitate further investigation. Additionally, the financial implications, accessibility, and feasibility of incorporating EECP into routine HFpEF care need a thorough evaluation. While promising, integrating EECP into HFpEF treatment algorithms should be approached with a nuanced understanding of these limitations, encouraging continued research to refine its role and maximize its potential within the HFpEF therapeutic landscape.

Future Directions

The encouraging potential of EECP in HFpEF management paves the way for future research endeavors. One promising direction involves the conduct of dedicated, well-designed clinical trials with a specific focus on HFpEF, aiming to establish robust evidence regarding the efficacy, safety, and optimal patient selection criteria for EECP in this particular subset of heart failure. Integrating advanced imaging techniques and biomarkers may enhance patient stratification and help identify individuals most likely to benefit from EECP. Moreover, investigating the long-term outcomes and durability of EECP in HFpEF management is crucial for understanding its sustained impact. Future research could also delve into the mechanical intricacies of how EECP influences the pathophysiological processes underlying HFpEF, providing insights into targeted interventions. Additionally, efforts to address logistical challenges, such as cost-effectiveness and accessibility, may contribute to the successful incorporation of EECP into routine HFpEF care. Overall, future directions should prioritize refining the evidence base, optimizing patient selection, and elucidating the nuanced role of EECP in the comprehensive management of HFpEF.

Conclusion

In conclusion, the comprehensive analysis of studies on External Extracorporeal Counterpulsation (EECP) underscores its potential as a therapeutic intervention in Heart Failure with Preserved Ejection Fraction (HFpEF). The research reveals promising outcomes in exercise capacity, symptomatic relief, and improvements in various cardiovascular parameters. EECP's mechanisms of action, spanning enhanced endothelial function, oxidative stress reduction, and angiogenesis promotion, offer valuable insights into its multifaceted impact. Despite these encouraging findings, limitations such as the need for further large-scale trials and protocol standardization should be acknowledged. Future research should focus on refining patient selection criteria, optimizing treatment regimens, and exploring the long-term impact of EECP in HFpEF. As the landscape of cardiovascular therapeutics evolves, EECP is a promising modality, warranting continued

investigation for its efficacy, safety, and potential integration into the holistic management of HFpEF.

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Conflict of interest

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References

1. ^*Toth PP, Gauthier D. Heart failure with preserved ejection fraction: disease burden for patients, caregivers, and the health-care system. Postgrad Med. 2021 Mar;133(2):140-145. doi: 10.1080/00325481.2020.1842621. Epub 2020 Nov 27. PMID: 33131371.*
2. a, b, c, d*Ma C, Luo H, Fan L, Liu X, Gao C. Heart failure with preserved ejection fraction: an update on pathophysiology, diagnosis, treatment, and prognosis. Braz J Med Biol Res. 2020 Jun 5;53(7):e9646. doi: 10.1590/1414-431X20209646. Erratum in: Braz J Med Biol Res. 2021 Feb 26;54(4):e9646erratum. PMID: 32520204; PMCID:PMC7296715.*
3. ^*Hajouli S, Ludhwani D. Heart Failure and Ejection Fraction. [Updated 2022 Dec 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553115/*
4. ^*Andersson C, Vasan RS. Epidemiology of heart failure with preserved ejection fraction. Heart Fail Clin. 2014 Jul;10(3):377-88. doi: 10.1016/j.hfc.2014.04.003. PMID: 24975902; PMCID: PMC4084609.*
5. a, b*Barsness GW. Enhanced External Counterpulsation in Unrevascularizable Patients. Curr Interv Cardiol Rep. 2001 Feb;3(1):37-43. PMID: 11177718.*
6. ^*Mielniczuk L, da Silva LB, Haddad H. Enhanced external counterpulsation in ischemic heart disease and congestive heart failure. CMAJ. 2004 Apr 13;170(8):1223-4. doi: 10.1503/cmaj.1031171. PMID: 15078841; PMCID: PMC385349.*
7. a, b, c, d, e, f, g, h*Sharma U, Ramsey HK, Tak T. The role of enhanced external counter pulsation therapy in clinical practice. Clin Med Res. 2013 Dec;11(4):226-32. doi: 10.3121/cmr.2013.1169. PMID: 24510321; PMCID: PMC3917995.*
8. a, b*Casey DP, Conti CR, Nichols WW, Choi CY, Khuddus MA, Braith RW. Effect of enhanced external counterpulsation on inflammatory cytokines and adhesion molecules in patients with angina pectoris and angiographic coronary artery disease. Am J Cardiol. 2008 Feb 1;101(3):300-2. doi: 10.1016/j.amjcard.2007.08.031. Epub 2007 Dec 11. PMID: 18237588; PMCID: PMC2276610.*
9. ^*Medical Advisory Secretariat. Enhanced External Counterpulsation (EECP): An Evidence-Based Analysis. Ont Health Technol Assess Ser. 2006;6(5):1-70. Epub 2006 Mar 1. PMID: 23074496; PMCID: PMC3379533.*

10. [a, b, c, d]*Subramanian R, Nayar S, Meyyappan C, Ganesh N, Chandrakasu A, Nayar PG. Effect of Enhanced External Counter Pulsation Treatment on Aortic Blood Pressure, Arterial Stiffness and Ejection Fraction in Patients with Coronary Artery Disease. J Clin Diagn Res. 2016 Oct;10(10):OC30-OC34. doi: 10.7860/JCDR/2016/23122.8743. Epub 2016 Oct 1. PMID: 27891374; PMCID: PMC5121712.*
11. [^]*Bozorgi A, Mehrabi Nasab E, Sardari A, Nejatian M, Nasirpour S, Sadeghi S. Effect of Enhanced External Counterpulsation (EECP) on Exercise Time Duration and Functional Capacity in Patients with Refractory Angina Pectoris. J Tehran Heart Cent. 2014 Jan 12;9(1):33-7. PMID: 25561968; PMCID: PMC4277789.*
12. [a, b]*Obokata M, Reddy YNV, Borlaug BA. Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction: Understanding Mechanisms by Using Noninvasive Methods. JACC Cardiovasc Imaging. 2020 Jan;13(1 Pt 2):245-257. doi: 10.1016/j.jcmg.2018.12.034. Epub 2019 Jun 12. PMID: 31202759; PMCID: PMC6899218.*
13. [a, b]*Caceres J, Atal P, Arora R, Yee D. Enhanced external counterpulsation: A unique treatment for the "No-Option" refractory angina patient. J Clin Pharm Ther. 2021 Apr;46(2):295-303. doi: 10.1111/jcpt.13330. Epub 2021 Jan 7. PMID: 33410549; PMCID: PMC7986429.*
14. [^]*Kitsou V, Xanthos T, Roberts R, Karlis GM, Padadimitriou L. Enhanced external counterpulsation: mechanisms of action and clinical applications. Acta Cardiol. 2010 Apr;65(2):239-47. doi: 10.2143/AC.65.2.2047060. PMID: 20458834.*
15. [^]*Bonetti PO, Barsness GW, Keelan PC, Schnell TI, Pumper GM, Kuvin JT, Schnall RP, Holmes DR, Higano ST, Lerman A. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. J Am Coll Cardiol. 2003 May 21;41(10):1761-8. doi: 10.1016/s0735-1097(03)00329-2. PMID: 12767662.*
16. [^]*Ambari AM, Lilihata G, Zuhri E, Ekawati E, Wijaya SA, Dwiputra B, Sukmawan R, Radi B, Haryana SM, Adiarto S, Hanafy DA, Zamroni D, Elen E, Mangkuanom AS, Santoso A. External Counterpulsation Improves Angiogenesis by Preserving Vascular Endothelial Growth Factor-A and Vascular Endothelial Growth Factor Receptor-2 but Not Regulating MicroRNA-92a Expression in Patients With Refractory Angina. Front Cardiovasc Med. 2021 Oct 25;8:761112. doi: 10.3389/fcvm.2021.761112. PMID: 34760951; PMCID: PMC8573065.*
17. [^]*Gevaert AB, Kataria R, Zannad F, Sauer AJ, Damman K, Sharma K, Shah SJ, Van Spall HGC. Heart failure with preserved ejection fraction: recent concepts in diagnosis, mechanisms and management. Heart. 2022 Aug 11;108(17):1342-1350. doi: 10.1136/heartjnl-2021-319605. PMID: 35022210.*
18. [^]*Lawson WE, Kennard ED, Holubkov R, Kelsey SF, Strobeck JE, Soran O, Feldman AM; IEPR investigators. Benefit and safety of enhanced external counterpulsation in treating coronary artery disease patients with a history of congestive heart failure. Cardiology. 2001;96(2):78-84. doi: 10.1159/000049088. PMID: 11740136.*
19. [^]*Abbottsmith CW, Chung ES, Varricchione T, de Lame PA, Silver MA, Francis GS, Feldman AM; Prospective Evaluation of EECP in Congestive Heart Failure Investigators. Enhanced external counterpulsation improves exercise duration and peak oxygen consumption in older patients with heart failure: a subgroup analysis of the PEECH trial. Congest Heart Fail. 2006 Nov-Dec;12(6):307-11. doi: 10.1111/j.1527-5299.2006.05904.x. PMID: 17170583.*
20. [a, b]*Feldman AM, Silver MA, Francis GS, Abbottsmith CW, Fleishman BL, Soran O, de Lame PA, Varricchione T; PEECH Investigators. Enhanced external counterpulsation improves exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol. 2006 Sep 19;48(6):1198-205. doi: 10.1016/j.jacc.2005.10.079. Epub 2006 Aug 28. PMID:*

16979005.

21. ^*Soran O, Kennard ED, Bart BA, Kelsey SF; IEPR Investigators. Impact of external counterpulsation treatment on emergency department visits and hospitalizations in refractory angina patients with left ventricular dysfunction. Congest Heart Fail. 2007 Jan-Feb;13(1):36-40. doi: 10.1111/j.1527-5299.2007.05989.x. Erratum in: Congest Heart Fail. 2007 Mar-Apr;13(2):124. PMID: 17268208.*
22. ^*Kozdağ G, Ertaş G, Aygün F, Emre E, Kirbaş A, Ural D, Soran O. Clinical effects of enhanced external counterpulsation treatment in patients with ischemic heart failure. Anadolu Kardiyol Derg. 2012 May;12(3):214-21. doi: 10.5152/akd.2012.064. Epub 2012 Feb 24. PMID: 22366105.*
23. ^*Arora RR, Shah AG. The role of enhanced external counterpulsation in the treatment of angina and heart failure. Can J Cardiol. 2007 Aug;23(10):779-81. doi: 10.1016/s0828-282x (07)70826-7. PMID: 17703254; PMCID: PMC2651381.*
24. ^*Prasad GN, Ramasamy S, Thomas JM, Nayar PG, Sankar MN, Sivakadaksham N, Cherian KM. Enhanced external counterpulsation (EECP) therapy: current evidence for clinical practice and who will benefit? Indian Heart J. 2010 Jul-Aug;62(4):296-302. PMID: 21280467.*
25. ^*Soran O, Fleishman B, Demarco T, Grossman W, Schneider VM, Manzo K, de Lame PA, Feldman AM. Enhanced external counterpulsation in patients with heart failure: a multicenter feasibility study. Congest Heart Fail. 2002 Jul-Aug;8(4):204-8, 227. doi: 10.1111/j.1527-5299.2002.01731.x. PMID: 12147943.*