UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WATSON LABORATORIES, INC.,
Petitioner

v.

UNITED THERAPEUTICS, INC.,
Patent Owner

Trial No. IPR2017-01622
Patent 9,339,507

DECLARATION OF SCOTT BENNETT, Ph.D.
20 June 2017

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I, Scott Bennett, hereby declare under penalty of perjury:

I. INTRODUCTION

1. I have personal knowledge of the facts and opinions set forth in this declaration, I believe them to be true, and if called upon to do so, I would testify competently to them. I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both.

2. I am a retired academic librarian working as a Managing Partner of the firm Prior Art Documentation LLC at 711 South Race Street, Urbana, IL, 61801-4132. Attached as Appendix A is a true and correct copy of my Curriculum Vitae describing my background and experience. Further information about my firm, Prior Art Documentation Services LLC, is available at www.priorartdocumentation.com.

3. I have been retained by Winston & Strawn LLP to authenticate and establish the dates of public accessibility of certain documents in an *inter partes* review proceedings for U.S. Patent No. 9,339,507. For this service, I am being paid my usual hourly fee of $91/hour. My compensation in no way depends on the substance of my testimony or the outcome of this proceeding.

II. BACKGROUND AND QUALIFICATIONS

4. I was previously employed as follows:

- University Librarian, Yale University, New Haven, CT, 1994-2001;

- Director, The Milton S. Eisenhower Library, The Johns Hopkins University, Baltimore, MD, 1989-1994;
- Assistant University Librarian for Collection Management, Northwestern University, Evanston, IL, 1981-1989;
- Instructor, Assistant, and Associate Professor of Library Administration, University of Illinois at Urbana-Champaign, Urbana, IL, 1974-1981; and
- Assistant Professor of English, University of Illinois at Urbana-Champaign, 1967-1974.

5. Over the course of my work as a librarian, professor of English, researcher, and author of nearly fifty scholarly papers and other publications, I have had extensive experience with catalog records and online library management systems built around Machine-Readable Cataloging (MARC) standards. I also have substantial experience in authenticating printed documents and establishing the date when they were accessible to researchers.

6. In the course of more than fifty years of academic life, I have myself been an active researcher. I have collaborated with many individual researchers and, as a librarian, worked in the services of thousands of researchers at four prominent research universities. Over the years, I have read some of the voluminous professional literature on the information seeking behaviors of

academic researchers. And as an educator, I have a broad knowledge of the ways in which students in a variety of disciplines learn to master the bibliographic resources used in their disciplines. In all of these ways, I have a general knowledge of how researchers work.

III. PRELIMINARIES

7. *Scope of this declaration*. I am not a lawyer and I am not rendering an opinion on the legal question of whether any particular document is, or is not, a "printed publication" under the law.

8. I am, however, rendering my expert opinion on the authenticity of the documents referenced herein and on when and how each of these documents was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, could have located the documents before 15 May 2005 and 15 May 2006.

9. *Materials considered*. In forming the opinions expressed in this declaration, I have reviewed the documents and attachments referenced herein. These materials are records created in the ordinary course of business by publishers, libraries, indexing services, and others. From my years of experience, I am familiar with the process for creating many of these records, and I know these records are created by people with knowledge of the information in the record. Further, these records are created with the expectation that researchers and other

members of the public will use them. All materials cited in this declaration and its attachments are of a type that experts in my field would reasonably rely upon and refer to in forming their opinions.

10. *Persons of ordinary skill in the art.* I am told by counsel that the subject matter of this proceeding relates to the administration of a drug called treprostinil to patients that have a condition called pulmonary hypertension. I have been further informed that the patent relates to the administration of inhaled doses of this drug using a device called a pulsed ultrasonic nebulizer, which I have been informed causes the drug to take on an aerosol form so that it can be inhaled by patients.

11. I have been informed by counsel that a "person of ordinary skill in the art at the time of the inventions" is a hypothetical person who is presumed to be familiar with the relevant field and its literature at the time of the inventions. This hypothetical person is also a person of ordinary creativity, capable of understanding the scientific principles applicable to the pertinent field.

12. I am told by counsel that persons of ordinary skill in this subject matter or art would have had a Ph.D. degree in pharmaceutical science or a related discipline like chemistry or medicinal chemistry, as well as at least two years of practical experience in the development of potential drug candidates, specifically in the delivery of drug by inhalation. I understand that this person could have a

lower level of formal education than a Ph.D. degree if such a person had more years of experience in the development of inhalable drugs. This person would regularly review literature about pharmaceutical sciences and drug delivery and would know how to carry out library research using library resources to find out more information about areas being researched. In addition, the person of ordinary skill in the art would know how to evaluate potential drugs for their in vitro and in vivo activity and toxicity using tests disclosed in the relevant literature. Furthermore, because drug development involves a multidisciplinary approach, I understand that a person of ordinary skill in the art may interface or consult with individuals having specialized expertise, for example, a pharmacologist and/or physician with experience in the administration, dosing and efficacy of drugs for the treatment of a particular disease state..

13. It is my opinion that such a person would have been engaged in advanced research starting at least in graduate school, learning though study and practice in the field and possibly through formal instruction the bibliographic resources relevant to his or her research. In the early 2000's such a person would have had access to a vast array of long-established print resources regarding medical conditions concerning the circulatory system, such as pulmonary hypertension. as well as access to a rich set of online resources providing indexing information, abstracts, and full text services for literature providing updates

regarding treatments for conditions of the circulatory system. Such information includes abstracts of presentations made at conferences, more comprehensive articles circulated in periodicals, and access to versions of such articles through paid Internet sites

14. *Library catalog records*. WorldCat is the world's largest public online catalog, maintained by the Online Computer Library Center, Inc., or OCLC, and built with the records created by the thousands of libraries that are members of OCLC. WorldCat records appear in many different catalogs, including the Statewide Illinois Library Catalog. The date a given catalog record was created (corresponding to the MARC Field 008) appears in some detailed WorldCat records as the Date of Entry.

15. *Publications in series*. A library typically creates a MARC catalog record for a series of closely related publications, such as the proceedings of an annual conference, when the library receives its first issue. When the institution receives subsequent issues/volumes of the series, the issues/volumes are checked in (sometimes using a date stamp), added to the institution's holdings records, and made available very soon thereafter—normally within a few days of receipt or (at most) within a few weeks of receipt.

16. The initial series record will often not reflect all of the subsequent changes in publication details (including minor variations in title, etc.).

17. When a library does not intend systematically to acquire all publications in a given series, but adds individual volumes of the series to its collections, the library will typically treat each such volume as an individual book, or monograph. In this case, the 008 Field MARC will record the date when the record for that individual volume, not the series, was created.

18. It is sometimes possible to find both a series and a monograph library catalog record for the same publication.

19. *Periodical publications*. A library typically creates a catalog record for a periodical publication when the library receives its first issue. When the institution receives subsequent issues/volumes of the periodical, the issues/volumes are checked in (often using a date stamp), added to the institution's holdings records, and made available very soon thereafter—normally within a few days of receipt or (at most) within a few weeks of receipt.

20. The initial periodicals record will sometimes not reflect all of the subsequent changes in publication details (including minor variations in title, etc.).

21. *Indexing*. A researcher may discover material relevant to his or her topic in a variety of ways. One common means of discovery is to search for relevant information in an index of periodical and other publications. Having found relevant material, the researcher will then normally obtain it online, look for it in libraries, or purchase it from the publisher, a bookstore, a document delivery

service, or other provider. Sometimes, the date of a document's public accessibility will involve both indexing and library date information. Date information for indexing entries is, however, often unavailable. This is especially true for online indices.

22. Indexing services use a wide variety of controlled vocabularies to provide subject access and other means of discovering the content of documents. The formats in which these access terms are presented vary from service to service.

23. Online indexing services commonly provide bibliographic information, abstracts, and full-text copies of the indexed publications, along with a list of the documents cited in the indexed publication. These services also often provide lists of publications that cite a given document. A citation of a document is evidence that the document was publicly available and in use by researchers no later than the publication date of the citing document.

24. Prominent indexing services include:

25. Scopus. Produced by Elsevier, a major publisher, Scopus is the largest database of abstracts and citations of peer-reviewed literature. Its scope includes the social sciences, science, technology, medicine, and the arts. It includes 60 million records from more than 21,500 titles from some 5,000 international publishers. Coverage includes 360 trade publications, over 530 book

series, more than 7.2 million conference papers, and 116,000 books. Records date from 1823.

IV. OPINIONS REGARDING INDIVIDUAL DOCUMENTS

Document 1. Robert Voswinckel, et al. "Inhaled trepostinil sodium for the treatment of pulmonary hypertension" Abstract #1414, *Circulation,* 110, 17, Supplement (October 2004): III-295.

1. Authentication

26. Document 1 is an abstract by Robert Voswinckel and others published in an October 2004 supplementary issue of Circulation. This supplement contains abstracts from Scientific Sessions 2004, a conference held by the American Heart Association in New Orleans, LA, on 7-10 November 2004.

27. Attachment 1a is a true and accurate copy of Document 1 (along with the volume cover, preliminary pages about the supplement and about Circulation) from the British Library. Attachment 1b is a true and accurate copy of the British Library catalog record for 2004 Abstracts supplement to Circulation.

28. Attachment 1a is in a condition that creates no suspicion about its authenticity. Specifically, Document 1 exhibits ample evidence of its publication provenance and is marked as supplied by the British Library. Attachment 1a was found within the custody of a library – a place where, if authentic, it would likely be found.

29. I conclude, based on finding Document 1 in a library and on finding library catalog records for Document 1, that Document 1 is an authentic document and that Attachment 1a is an authentic copy of Document 1.

2. Public Accessibility

30. Attachment 1c is a true and accurate copy of the Statewide Illinois Library Catalog periodical record for Circulation, showing this periodical was first published in 1950 and is held by 1,265 libraries world-wide. Attachment 1c also indicates that Circulation was cataloged or indexed in a meaningful way—including being cataloged by subject. Some libraries have separately cataloged the supplements to Circulation. Attachment 1d is a true and accurate copy of such a record from the Statewide Illinois Library Catalog, showing these abstract supplements were first published in 1964 and are held as separately cataloged documents by 20 libraries world-wide. Attachment 1d also indicates that the abstract supplements to Circulation were cataloged or indexed in a meaningful way—including being cataloged by subject, Thus, in my opinion, Circulation and its abstract supplements were sufficiently accessible to the public interested in the art; and an ordinarily skilled researcher, exercising reasonable diligence, would have had no difficulty finding copies of Circulation and its abstract supplements.

31. Attachment 1a, from the British Library, includes a library date label at the top of the cover. This date label was cropped in the process of copying the

cover at the British Library. Attachment 1e is a second copy of Document 1 from the British Library, supplied by counsel. Comparison of Attachment 1a and 1e reveals them to be substantively identical. The date label at the top of the cover indicates that the supplement to the October 2004 issue of Circulation was processed on 22 November 2004. A separate date label in the middle of the cover also shows this 22 November 2004 date. A third label on the cover indicates that the restriction on reading-room only use of the supplement to the October 2004 issue of Circulation expired on 22 May 2005. Based on my experience, I affirm this date label has the general appearance of date labels that libraries have long affixed to periodicals in processing them. I do not see any indications or have any reason to believe this date label was affixed by anyone other than library personnel on or about the date indicated by the label.

32. Allowing for some time between the date label on the supplement to the October 2004 issue of Circulation and its appearance on library shelves, where it would be publicly available (for example in the reading room at the British Library for a limited time, and then available for circulation), it is my opinion that Document 1 was publicly available at least by December 2004.

33. Attachment 1f is a true and accurate copy of the Scopus index record for a review article that cites Document 1: R. Sulica and M. Poon, "Medical therapeutics for pulmonary arterial hypertension: from basic science and clinical

trial design to evidence-based medicine," Expert Review of Cardiovascular Therapy, 3,3 (March 2005): 347-360 Attachment 1f shows Document 1 as the 51th item in its list of references.

3. Conclusion

34. Based on the evidence presented here—publication in a supplement to a widely held periodical, library processing, and citation—**it is my opinion that Document 1 is an authentic document that was publicly available to researchers at least by December 2004.** The citation evidence presented here indicates that Document 1 had been actually reviewed and cited to by researchers at least by March 2005

Document 2. Hossein Ardeschi Ghofani, Robert Voswinckel, et al., "Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie," Herz, 30,4 (June 2005): 296-302.

1. **Authentication**

35. Document 2 is a research paper by Hossein Ghofani, Robert Voswinckel, and others published in the June 2005 issue of Herz.

36. Attachment 2a is a true and accurate copy of Document 2 (along with the cover, issue title page, and issue contents page) from the Biomedical Library at the University of California at Los Angeles. Attachment 2b is a true and accurate copy of the University of California at Los Angeles Library catalog record for Herz, showing holdings that include Volume 30 of this periodical.

37. Attachment 2a is in a condition that creates no suspicion about its authenticity. Specifically, Document 2 is not missing any intermediate pages of the article's text, the text on each page appears to flow seamlessly from one page to the next, and there are no visible alterations to the document. Attachment 2a was found within the custody of a library – a place where, if authentic, it would likely be found.

38. Document 2 is also readily available online. Attachment 2c is a true and accurate copy of the table of contents for the June 2005 issue of Herz, including Document 2, from SpringerLink, the online source for journals published by Springer Publishing, including Herz. Attachment 2d is a true and accurate copy of Document 2 from SpringerLink—a place where, if authentic, Document 2 would likely be found.

39. Attachment 2e is the Scopus record for Document 2, showing the many indexed keywords by which an ordinarily skilled researcher, exercising reasonable diligence, could find Document 2.

40. I conclude, based on finding Document 2 in a library and online and on finding library catalog records and online records for Document 2, that Document 2 is an authentic document and that Attachment 2a is an authentic copy of Document 2.

2. **Public Accessibility**

41. Attachment 2f is a true and accurate copy of the Statewide Illinois Library Catalog record for Herz, showing this periodical was first published in 1976 and is held by 97 libraries world-wide. Attachment 2f also indicates that Herz was cataloged or indexed in a meaningful way—including being cataloged by subject. Thus, in my opinion, Herz was sufficiently accessible to the public interested in the art; and an ordinarily skilled researcher, exercising reasonable diligence, would have had no difficulty finding copies of Herz.

42. Attachment 2a, from the University of California Library at Los Angeles, includes a library date stamp indicating that the June 2005 issue of Herz was processed on 22 June 2005. Based on my experience, I affirm this date stamp has the general appearance of date stamps that libraries have long affixed to periodicals in processing them. I do not see any indications or have any reason to believe this date stamp was affixed by anyone other than library personnel on or about the date indicated by the stamp.

43. Allowing for some time between the date stamp on the June 2005 issue of Herz and its appearance on library shelves, where it would be publicly available, it is my opinion that Document 2 was publicly available at least by early-July 2005.

3. Conclusion

44. Based on the evidence presented here—publication in the widely held periodical, library catalog records, online indexing and publication, library processing, and citation—**it is my opinion that Document 2 is an authentic document that was publicly available to researchers at least by early July 2005.**

V. ATTACHMENTS

45. The attachments attached hereto are true and correct copies of the materials identified above. Helen Sullivan is a Managing Partner in Prior Art Documentation Services LLC (see http://www.priorartdocumentation.com/hellen-sullivan/). One of her primary responsibilities in our partnership is to secure the bibliographic documentation used in attachments to our declarations.

46. Ms. Sullivan and I work in close collaboration on the bibliographic documentation needed in each declaration. I will sometimes request specific bibliographic documents or, more rarely, secure them myself. In all cases, I have carefully reviewed the bibliographic documentation used in my declaration. My signature on the declaration indicates my full confidence in the authenticity, accuracy, and reliability of the bibliographic documentation used.

47. Each Attachment has been marked with an identifying label on the top of each page. However, no alterations other than these noted labels appear in these

attachments, unless otherwise noted. All attachments were created on 9-16 June and all URLs referenced in this declaration were available 16 June 2017.

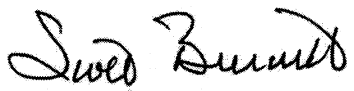
VI. CONCLUSION

48. In summary, I have concluded that Document 1, discussed above, is an authentic document that was publicly accessible before 15 May 2005. I further conclude that Document 2, discussed above, is an authentic document that was publicly accessible before 15 May 2006.

49. I reserve the right to supplement my opinions in the future to respond to any arguments that Patent Owner or its expert(s) may raise and to take into account new information as it becomes available to me.

50. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed this 20th day of June, 2017 in Urbana, Illinois.



Scott Bennett

Appendix A

SCOTT BENNETT
Yale University Librarian Emeritus

711 South Race
Urbana, Illinois 61801-4132
2scottbb@gmail.com
217-367-9896

EMPLOYMENT

Retired, 2001. Retirement activities include:

- Managing Partner in Prior Art Documentation Services, LLC, 2015-. This firm provides documentation services to patent attorneys; more information is available at http://www.priorartdocumentation.com
- Consultant on library space design, 2004- . This consulting practice is rooted in a research, publication, and public speaking program conducted since I retired from Yale University in 2001. I have served more than 50 colleges and universities in the United States and abroad with projects ranging in likely cost from under $50,000 to over $100 million. More information is available at http://www.libraryspaceplanning.com/
- Senior Advisor for the library program of the **Council of Independent Colleges**, 2001-2009
- Member of the Wartburg College Library Advisory Board, 2004-
- Visiting Professor, Graduate School of Library and Information Science, **University of Illinois at Urbana-Champaign**, Fall 2003

University Librarian, **Yale University**, 1994-2001

Director, The Milton S. Eisenhower Library, **The Johns Hopkins University**, Baltimore, Maryland, 1989-1994

Assistant University Librarian for Collection Management, **Northwestern University**, Evanston, Illinois, 1981-1989

Instructor, Assistant and Associate Professor of Library Administration, **University of Illinois at Urbana-Champaign**, 1974-1981

Assistant Professor of English, **University of Illinois at Urbana-Champaign**, 1967-1974

Woodrow Wilson Teaching Intern, **St. Paul's College**, Lawrenceville, Virginia, 1964-1965

EDUCATION

University of Illinois, M.S., 1976 (Library Science)
Indiana University, M.A., 1966; Ph.D., 1967 (English)
Oberlin College, A.B. magna cum laude, 1960 (English)

HONORS AND AWARDS

Morningside College (Sioux City, IA) Doctor of Humane Letters, 2010

American Council of Learned Societies Fellowship, 1978-1979; Honorary Visiting Research Fellow, Victorian Studies Centre, **University of Leicester**, 1979; **University of Illinois** Summer Faculty Fellowship, 1969

Indiana University Dissertation Year Fellowship and an **Oberlin College** Haskell Fellowship, 1966-1967; **Woodrow Wilson** National Fellow, 1960-1961

PROFESSIONAL ACTIVITIES

American Association for the Advancement of Science: Project on Intellectual Property and Electronic Publishing in Science, 1999-2001

American Association of University Professors: University of Illinois at Urbana-Champaign Chapter Secretary and President, 1975-1978; Illinois Conference Vice President and President, 1978-1984; national Council, 1982-1985, Committee F, 1982-1986, Assembly of State Conferences Executive Committee, 1983-1986, and Committee H, 1997-2001 ; Northwestern University Chapter Secretary/Treasurer, 1985-1986

Association of American Universities: Member of the Research Libraries Task Force on Intellectual Property Rights in an Electronic Environment, 1993-1994, 1995-1996

Association of Research Libraries: Member of the Preservation Committee, 1990-1993; member of the Information Policy Committee, 1993-1995; member of the Working Group on Copyright, 1994-2001; member of the Research Library Leadership and Management Committee, 1999-2001; member of the Board of Directors, 1998-2000

Carnegie Mellon University: Member of the University Libraries Advisory Board, 1994

Center for Research Libraries: Program Committee, 1998-2000

Johns Hopkins University Press: Ex-officio member of the Editorial Board, 1990-1994; Co-director of Project Muse, 1994

Library Administration and Management Association, Public Relations Section, Friends of the Library Committee, 1977-1978

Oberlin College: Member of the Library Visiting Committee, 1990, and of the Steering Committee for the library's capital campaign, 1992-1993; President of the Library Friends, 1992-1993, 2004-2005; member, Friends of the Library Council, 2003-

Research Society for Victorian Periodicals: Executive Board, 1971-1983; Co-chairperson of the Executive Committee on Serials Bibliography, 1976-1982; President, 1977-1982

A Selected Edition of W.D. Howells (one of several editions sponsored by the MLA Center for Editions of American Authors): Associate Textual Editor, 1965-1970; Center for Editions of American Authors panel of textual experts, 1968-1970

Victorian Studies: Editorial Assistant and Managing Editor, 1962-1964

Wartburg College: member, National Advisory Board for the Vogel Library, 2004-

Some other activities: Member of the **Illinois State Library** Statewide Library and Archival Preservation Advisory Panel; member of the **Illinois State Archives** Advisory Board; member of a committee advising the **Illinois Board of Higher Education** on the cooperative management of research collections; chair of a major collaborative research project conducted by the **Research Libraries Group** with support from Conoco, Inc.; active advisor on behalf of the **Illinois Conference AAUP** to faculty and administrators on academic freedom and tenure matters in northern Illinois.

Delegate to **Maryland Governor's Conference on Libraries and Information Service**; principal in initiating state-wide preservation planning in Maryland; principal in an effort to widen the use of mass deacidification for the preservation of library materials through cooperative action by the **Association of Research Libraries** and the **Committee on Institutional Cooperation**; co-instigator of a campus-wide information service for **Johns Hopkins University**; initiated efforts with the **Enoch Pratt Free Library** to provide information services to Baltimore's Empowerment Zones; speaker or panelist on academic publishing, copyright, scholarly communication, national and regional preservation planning, mass deacidification.

Consultant for the **University of British Columbia** (1995), **Princeton University** (1996), **Modern Language Association**, (1995, 1996), **Library of Congress** (1997), **Center for Jewish History** (1998, 2000-), **National Research Council** (1998); Board of Directors for the **Digital Library Federation**, 1996-2001; accreditation visiting team at **Brandeis University** (1997); mentor for **Northern Exposure to Leadership** (1997); instructor and mentor for ARL's **Leadership and Career Development Program** (1999-2000)

At the **Northwestern University Library**, led in the creation of a preservation department and in the renovation of the renovation, for preservation purposes, of the Deering Library book stacks.

At the **Milton S. Eisenhower Library**, led the refocusing and vitalization of client-centered services; strategic planning and organizational restructuring for the library; building renovation planning. Successfully completed a $5 million endowment campaign for the humanities collections and launched a $27 million capital campaign for the library.

At the **Yale University Library**, participated widely in campus-space planning, university budget planning, information technology development, and the promotion of effective teaching and learning; for the library has exercised leadership in space planning and renovation, retrospective conversion of the card catalog, preservation, organizational development, recruitment of minority librarians, intellectual property and copyright issues, scholarly communication, document delivery services among libraries, and instruction in the use of information resources. Oversaw approximately $70 million of library space renovation and construction. Was co-principal investigator for a grant to plan a digital archive for Elsevier Science.

Numerous to invitations speak at regional, national, and other professional meetings and at alumni meetings. Lectured and presented a series of seminars on library management at the **Yunnan University Library**, 2002. Participated in the 2005 International Roundtable for Library and Information Science sponsored by the **Kanazawa Institute of Technology** Library Center and the Council on Library and Information Resources.

PUBLICATIONS

"Putting Learning into Library Planning," *portal: Libraries and the Academy*, 15, 2 (April 2015), 215-231.

"How librarians (and others!) love silos: Three stories from the field " available at the Learning Spaces Collaborary Web site, http://www.pkallsc.org/

"Learning Behaviors and Learning Spaces," *portal: Libraries and the Academy,* 11, 3 (July 2011), 765-789.

"Libraries and Learning: A History of Paradigm Change," *portal: Libraries and the Academy,* 9, 2 (April 2009), 181-197. Judged as the best article published in the 2009 volume of *portal.*

"The Information or the Learning Commons: Which Will We Have?" *Journal of Academic Librarianship*, 34 (May 2008), 183-185. One of the ten most-cited articles published in JAL, 2007-2011.

"Designing for Uncertainty: Three Approaches," *Journal of Academic Librarianship*, 33 (2007), 165–179.

"Campus Cultures Fostering Information Literacy," *portal: Libraries and the Academy*, 7 (2007), 147-167. Included in Library Instruction Round Table Top Twenty library instruction articles published in 2007

"Designing for Uncertainty: Three Approaches," *Journal of Academic Librarianship*, 33 (2007), 165–179.

"First Questions for Designing Higher Education Learning Spaces," *Journal of Academic Librarianship*, 33 (2007), 14-26.

"The Choice for Learning," *Journal of Academic Librarianship*, 32 (2006), 3-13.

With Richard A. O'Connor, "The Power of Place in Learning," *Planning for Higher Education*, 33 (June-August 2005), 28-30

"Righting the Balance," in *Library as Place: Rethinking Roles, Rethinking Space* (Washington, DC: Council on Library and Information Resources, 2005), pp. 10-24

Libraries Designed for Learning (Washington, DC: Council on Library and Information Resources, 2003)

"The Golden Age of Libraries," in *Proceedings of the International Conference on Academic Librarianship in the New Millennium: Roles, Trends, and Global Collaboration*, ed. Haipeng Li (Kunming: Yunnan University Press, 2002), pp. 13-21. This is a slightly different version of the following item.

"The Golden Age of Libraries," *Journal of Academic Librarianship*, 24 (2001), 256-258

"Second Chances. An address . . . at the annual dinner of the Friends of the Oberlin College Library November 13 1999," Friends of the Oberlin College Library, February 2000

"Authors' Rights," *The Journal of Electronic Publishing* (December 1999), http://www.press.umich.edu/jep/05-02/bennett.html

"Information-Based Productivity," in *Technology and Scholarly Communication*, ed. Richard Ekman and Richard E. Quandt (Berkeley, 1999), pp. 73-94

"Just-In-Time Scholarly Monographs: or, Is There a Cavalry Bugle Call for Beleaguered Authors and Publishers?" *The Journal of Electronic Publishing* (September 1998), http://www.press.umich.edu/jep/04-01/bennett.html

"Re-engineering Scholarly Communication: Thoughts Addressed to Authors," *Scholarly Publishing*, 27 (1996), 185-196

"The Copyright Challenge: Strengthening the Public Interest in the Digital Age," *Library Journal*, 15 November 1994, pp. 34-37

"The Management of Intellectual Property," *Computers in Libraries*, 14 (May 1994), 18-20

"Repositioning University Presses in Scholarly Communication," *Journal of Scholarly Publishing*, 25 (1994), 243-248. Reprinted in *The Essential JSP. Critical Insights into the World of Scholarly Publishing. Volume 1: University Presses* (Toronto: University of Toronto Press, 2011), pp. 147-153

"Preservation and the Economic Investment Model," in *Preservation Research and Development. Round Table Proceedings, September 28-29, 1992*, ed. Carrie Beyer (Washington, D.C.: Library of Congress, 1993), pp. 17-18

"Copyright and Innovation in Electronic Publishing: A Commentary," *Journal of Academic Librarianship*, 19 (1993), 87-91; reprinted in condensed form in *Library Issues: Briefings for Faculty and Administrators*, 14 (September 1993)

with Nina Matheson, "Scholarly Articles: Valuable Commodities for Universities," *Chronicle of Higher Education*, 27 May 1992, pp. B1-B3

"Strategies for Increasing [Preservation] Productivity," *Minutes of the [119th] Meeting [of the Association of Research Libraries]* (Washington, D.C., 1992), pp. 39-40

"Management Issues: The Director's Perspective," and "Cooperative Approaches to Mass Deacidification: Mid-Atlantic Region," in *A Roundtable on Mass Deacidification*, ed. Peter G. Sparks (Washington, D.C.: Association of Research Libraries, 1992), pp. 15-18, 54-55

"The Boat that Must Stay Afloat: Academic Libraries in Hard Times," *Scholarly Publishing*, 23 (1992), 131-137

"Buying Time: An Alternative for the Preservation of Library Material," ACLS *Newsletter*, Second Series 3 (Summer, 1991), 10-11

"The Golden Stain of Time: Preserving Victorian Periodicals" in *Investigating Victorian Journalism*, ed. Laurel Brake, Alex Jones, and Lionel Madden (London: Macmillan, 1990), pp. 166-183

"Commentary on the Stephens and Haley Papers" in *Coordinating Cooperative Collection Development: A National Perspective*, an issue of *Resource Sharing and Information Networks*, 2 (1985), 199-201

"The Editorial Character and Readership of *The Penny Magazine*: An Analysis," *Victorian Periodicals Review*, 17 (1984), 127-141

"Current Initiatives and Issues in Collection Management," *Journal of Academic Librarianship*, 10 (1984), 257-261; reprinted in *Library Lit: The Best of 85*

"Revolutions in Thought: Serial Publication and the Mass Market for Reading" in *The Victorian Periodical Press: Samplings and Soundings*, ed. Joanne Shattock and Michael Wolff (Leicester: Leicester University Press, 1982), pp. 225-257

"Victorian Newspaper Advertising: Counting What Counts," *Publishing History*, 8 (1980), 5-18

"Library Friends: A Theoretical History" in *Organizing the Library's Support: Donors, Volunteers, Friends*, ed. D.W. Krummel, Allerton Park Institute Number 25 (Urbana: University of Illinois Graduate School of Library Science, 1980), pp. 23-32

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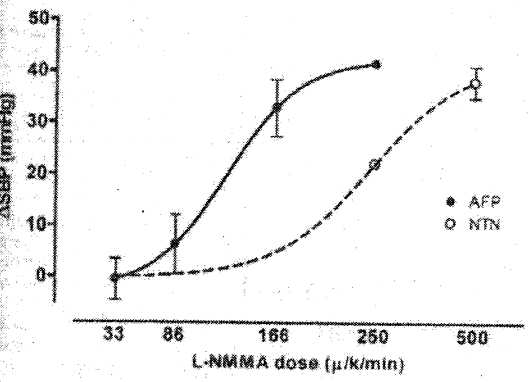
of membranous RhoA and phosphorylated ERM in brainstem were greater both in angiotensin II-treated rats and SHR than in WKY. Valsartan reduced the expression levels of membranous RhoA in angiotensin II-treated rats and SHR. In addition, Y-27632 or valsartan reduced the expression levels of phosphorylated ERM in both groups. Subcutaneous infusion of phenylephrine increased SBP to the same level of angiotensin II infusion in WKY. However, it did not alter the expression levels of membranous RhoA and phosphorylated ERM. Conclusions: These results suggest that 1) the pressor response induced by central infusion of angiotensin II is substantially mediated by activation of Rho/Rho-kinase pathway in brainstem via AT1 receptors, 2) this pathway may also be involved in hypertensive mechanism in SHR.

1412

Endothelial Nitric Oxide and Hypertension in Autonomic Failure

Alfredo Gamboa, Cyndya Shibao, Andre Diedrich, Bonnie K Black, Ginnie Farley, Satish R Raj, David Robertson, Italo Biaggioni; Vanderbilt Univ, Nashville, TN

More than half of patients with autonomic failure (AF) have severe supine hypertension despite low or unresponsive norepinephrine levels and often undetectable plasma renin activity. Supine hypertension is related to increased vascular resistance but the mechanism is not known. To test the hypothesis that nitric oxide deficiency contributes to supine hypertension we blocked endogenous nitric oxide synthase with L-NMMA in 5 AF patients and 7 normal controls (supine SBP 173±6 and 107±5 mmHg, respectively). Systolic blood pressure (SBP) was normalized to 110 mmHg in AF with graded head-up tilt, and barorefloxes were eliminated with trimethaphan in normal controls to mimic autonomic failure. The pressor response to graded doses of L-NMMA was shifted to the left in AF (Figure); The dose necessary to increase SBP by 30 mmHg was 3.4-fold lower in AF compared to controls (136±24 and 465±103 μg/k/min respectively, $p<0.02$). In conclusion, contrary to our original hypothesis, our results suggest an increased tonic release of nitric oxide in AF. Thus, NO deficiency does not contribute to supine hypertension in autonomic failure. On the contrary, this enhanced tonic NO may contribute to orthostatic hypotension in these patients.



1413

Oral Administration of a Mineralocorticoid Receptor Antagonist Reduces Brain, Heart, and Blood-borne Proinflammatory Cytokines in Heart Failure

Yu-Ming Kang, Carver College of Med, Univ of Iowa, Iowa City, IA; Ralph F Johnson, Univ of Iowa, Iowa City, IA; Zhi-Hua Zhang, Carver College of Med, Univ of Iowa, Iowa City, IA; Robert M Weiss, Carver College of Med, Univ of Iowa and VA Med Ctr, Iowa City, IA; Alan K Johnson, Univ of Iowa, Iowa City, IA; Robert B Felder; Carver College of Med, Univ of Iowa and VA Med Ctr, Iowa City, IA

Introduction: Brain and blood-borne cytokines may contribute to neurohumoral excitation in heart failure (HF). We previously reported that blockade of mineralocorticoid receptors (MR) in the central nervous system with spironolactone (SL) reduces circulating tumor necrosis factor (TNF)-α in HF rats. The effect of SL on proinflammatory cytokines (PIC) in the brain and on other important circulating PIC - interleukin (IL)-1β and IL-6 - was not determined. **Hypothesis:** Chronic treatment with oral SL will reduce brain and blood-borne PIC in rats with HF following MI. **Methods and Results:** Rats underwent coronary artery ligation to induce MI (48.2±2.0% of left ventricle, with ejection fraction of 35.5±4.1% by echocardiography), or sham surgery (SHAM). Six weeks later, immunohistochemistry of the paraventricular nucleus (PVN) of hypothalamus, a region critical to cardiovascular regulation, revealed more PVN neurons (MI vs SHAM, **P<0.01) positive for TNF-α (59.5±3.3** vs 10.8±0.9) and IL-1β (70.7±3.9** vs 13.8±1.2) in MI (n=6) than in SHAM (n=6) rats. Double staining demonstrated that these neurons were distributed among PVN neurons expressing Fra-like immunoreactivity, indicating chronic neuronal activation. MI rats (n=6) treated with SL (1 mg/kg/day orally for 6 weeks) had fewer (MI+SL vs MI, #P<0.01) Fra-like positive PVN neurons (85.5±5.4# vs 183.8±5.0), and fewer PVN neurons positive for TNF-α (22.4±1.8%# vs 32.4±1.7%) and IL-1β (19.1±1.3%# vs 38.4±2.1%). Levels of TNF-α, IL-1β and IL-6 in brain and heart tissues and in plasma were also lower in MI rats treated with SL (see table). **Conclusion:** In rats with ischemia-induced heart failure, orally administered SL has a global inhibitory influence on the appearance of proinflammatory cytokines in brain, heart and plasma. The beneficial influence of MR antagonism in patients with HF may result at least in part from blocking aldosterone-induced cytokine synthesis. (Table: *P<0.05 MI+SL vs MI+VEH)

Group	plasma IL-1β (pg/ml)	plasma IL-6 (pg/ml)	heart IL-1β (pg/mg protein)	hypothalamus IL-1β (pg/mg protein)	hypothalamus TNF-α (pg/mg protein)	brainstem TNF-α (pg/mg protein)	brainstem IL-6 (pg/mg protein)	cortex IL-1β (pg/mg protein)	heart/BW Ratio (mg/g)	lung/BW Ratio (mg/g)
MI+VEH (n=7)	131.1±10.9	119.5±9.7	53.4±6.5	47.1±7.9	8.3±0.7	9.1±0.9	67.1±10.1	26.4±4.1	7.2±0.2	13.5±0.9
MI+SL (n=7)	67.3±8.1*	53.3±8.6*	32.6±5.9*	29.4±3.1*	3.8±0.6*	2.8±0.3*	39.4±5.3*	25.8±5.2	6.4±0.3*	12.1±0.6*
SHAM+SL (n=6)	48.2±3.6	33.7±2.8	23.7±5.5	17.4±4.8	2.8±0.7	2.1±0.6	25.2±4.8	24.3±4.9	3.3±0.1	5.2±0.3
SHAM+VEH (n=6)	53.8±2.4	38.1±2.5	27.8±3.4	16.8±4.0	3.2±0.9	2.4±0.5	28.0±8.7	23.8±6.5	3.4±0.1	5.1±0.3

Pulmonary Arterial Hypertension: New Therapies

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1414

Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension

Robert Voswinckel, Beate Enke, Andre Kreckel, Frank Reichenberger, Stefanie Krick, Henning Gall, Tobias Gessler, Thomas Schmehl, Markus G Kohstall, Friedrich Grimminger, Hossein A Ghofrani, Werner Seeger, Horst Olschewski; Univ Hosp Giessen, Giessen, Germany

Objective: To evaluate the effects of inhaled TRE on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension (PH) and to assess safety, tolerability and clinical efficacy in patients with severe PH. **Background:** TRE is a stable prostacyclin analogue that has been approved for treatment of pulmonary arterial hypertension as a continuous subcutaneous infusion. Iloprost, another prostacyclin analogue, has been shown to be efficacious in a randomised controlled study as repetitive inhalation. **Methods:** In an open-label study a preservative free solution of inhaled TRE was applied to 17 patients with severe pulmonary hypertension during Swan-Ganz catheter investigation. Patients received a TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 μg/ml). Hemodynamics were observed for 2 hours. Two patients with idiopathic PAH received compassionate treatment with 4 inhalations of TRE per day after the acute test. **Results:** Patients (male/female= 4/13) suffered from iPAH (n=5), PAH other (n=8) and CTEPH (n=4); PVR 948 ± 112 dyn*s*cm^{-5}, PAP 48.3 ± 2.7 mmHg, PAWP 8.9 ± 0.5 mmHg, CVP 10.8 ± 1.6 mmHg, CO 3.8 ± 0.3 l/min, SvO2 61.8 ± 1.8 %. TRE inhalation resulted in a sustained, highly pulmonary selective vasodilatation over 120 minutes. Maximum PVR decrease was -31.2 ± 4.5 % after 30 min. PVR and SVR at 120 minutes after inhalation were 89.2 ± 4.2 % and 101.0 ± 4.0 % of the baseline values, respectively. The AUC for the observation period (120min) was -22.9 ± 3.8 % for PVR and -4.9 ± 3.2% for SVR. The compassionate use patients have been treated for more than 3 months. In both patients NYHA class improved (from IV to III and from III to II), and six minute walk increased (from 0 m (bedridden) to 143 m, and from 310 m to 486 m, respectively). No side effects have been observed by the patients during long-term treatment. **Conclusion:** Inhaled TRE shows strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing. Tolerability is excellent even at high drug concentrations and short inhalation times (3 breaths). Long-term treatment effects are very promising. The current results warrant controlled studies investigating this approach in a larger series of patients. Supported by Lung RX

1415

Rho-kinase in Pulmonary Hypertension

Ken Ishikura, Norikazu Yamada, Akihiro Tsuji, Satoshi Ota, Mashio Nakamura, Masaaki Ito, Naoki Isaka, Takeshi Nakano; Mie Univ Sch of Med, Tsu, Japan

Objectives: Pulmonary hypertension (PH) is a poor prognostic disease with limited treatment. Rho-kinase is involved in the pathophysiology of several diseases underlying smooth muscle hypercontraction. But the role of is unknown. The purpose of this preliminary report was to indicate the efficacy of fasudil, a Rho-kinase inhibitor in patients with pulmonary hypertension using interventional hemodynamic assessment. Methods: Fasudil was intravenously injected in 10 patients (9 female, mean ± SD, 46 ± 15 years, NYHA II n=2, III n=7, IV n=1) with primary (n=5) and secondary (n=5) PH who were not received any vasodilator. Fasudil was administrated 30mg with 1mg/min. Hemodynamic data were measured using Swan-Ganz catheter until 60 minutes after starting administration of fasudil. Hemodynamic and arterial blood gas data of baseline and the lowest total pulmonary resistance (TPR) time were compared. Results: The lowest TPR time was within 30 to 60 minutes after administration. Administration of fasudil significantly decreased TPR from 13.6 ± 6.8 U to 10.3 ± 4.9 U (-23.2 ± 9.2 %, $p < 0.001$) and mean pulmonary arterial pressure (mPAP) from 43.6 ± 14.5 mmHg to 38.8 ± 13.9 mmHg (-11.6 ± 10.4 %, $p < 0.02$). Cardiac index (CI) was significantly increased from 2.39 ± 0.86 L/min/m^2 to 2.74 ± 0.73 L/min/m^2 (+16.5 ± 15.1 %, $p < 0.01$). Although TPR was equally decreased in both primary and secondary PH, the changes in the parameters that prescribed TPR, namely CI and mPAP, were different between the two groups subjects. Increased CI was a major factor into reducing TPR in primary PH, while reduced mPAP

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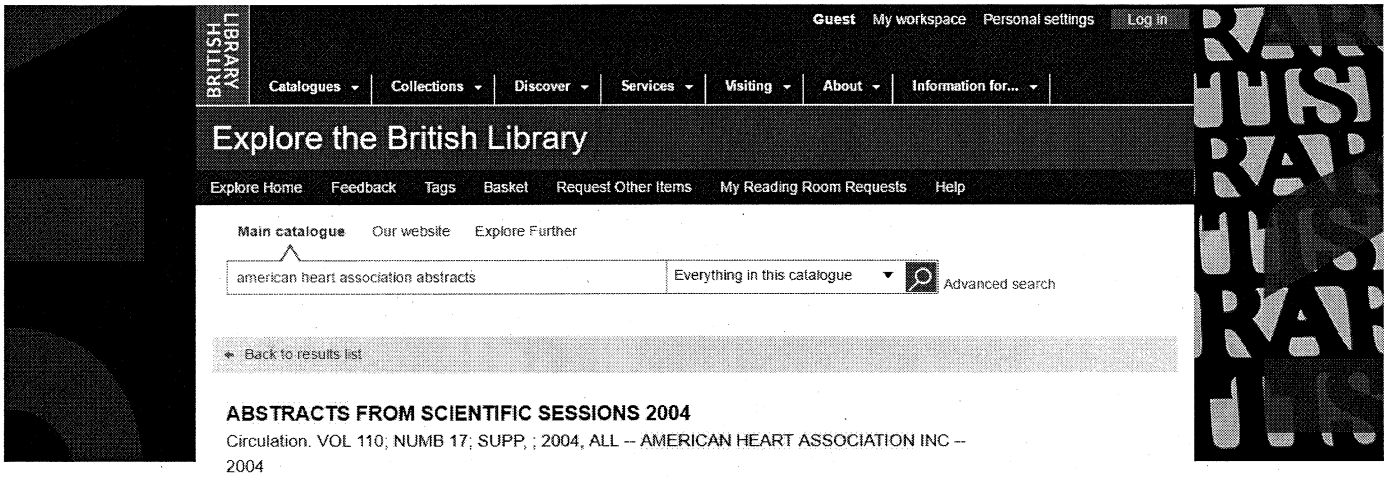

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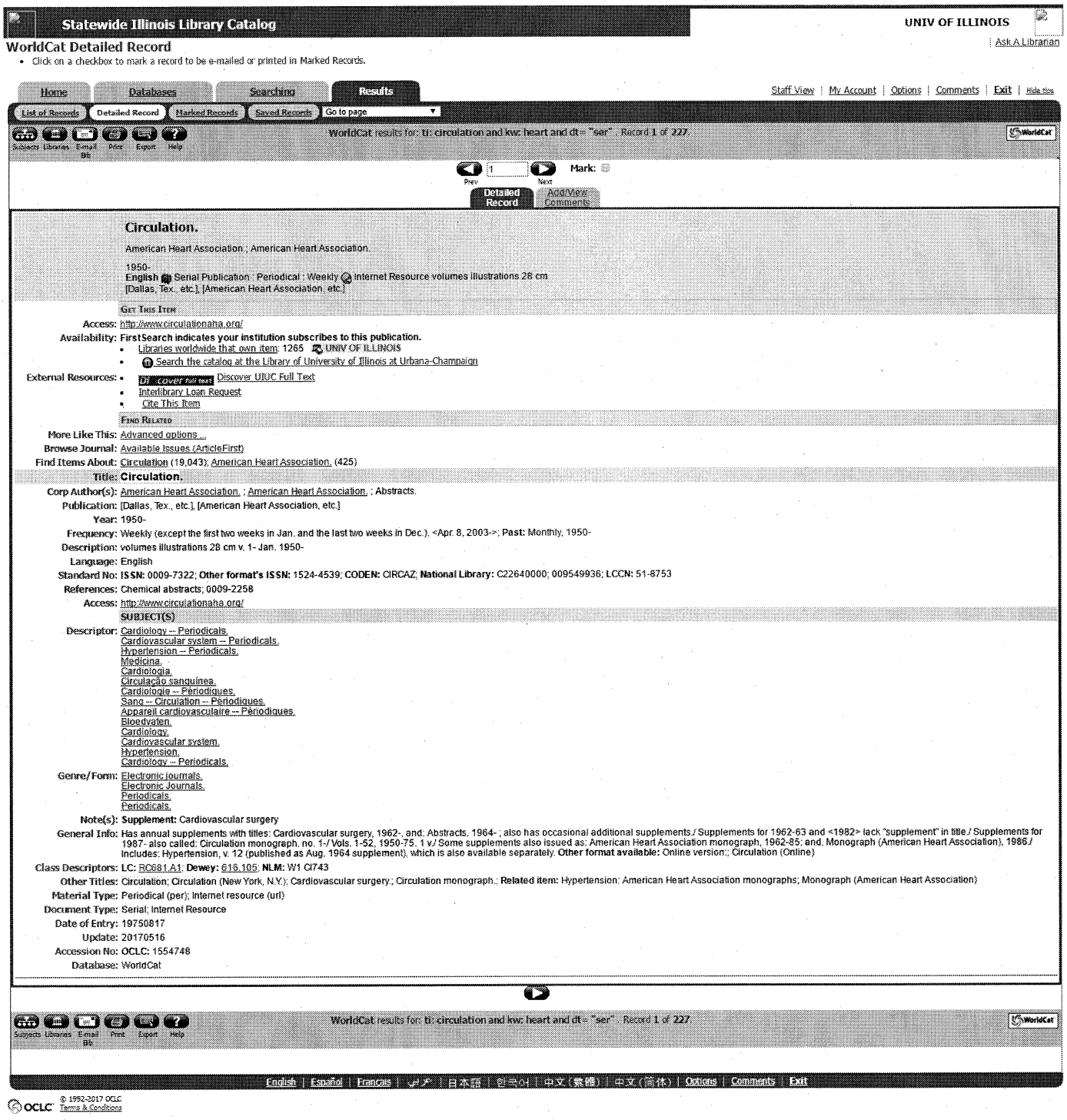

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Electronic Journals.
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Note(s): **Supplement:** Cardiovascular surgery

General Info: Has annual supplements with titles: Cardiovascular surgery, 1962-, and: Abstracts, 1964- ; also has occasional additional supplements./ Supplements for 1962-63 and <1982> lack "supplement" in title./ Supplements for 1987- also called: Circulation monograph, no. 1-/ Vols. 1-52, 1950-75. 1 v./ Some supplements also issued as: American Heart Association monograph, 1962-85; and, Monograph (American Heart Association), 1986./ Includes: Hypertension, v. 12 (published as Aug. 1964 supplement), which is also available separately. **Other format available:** Online version:; Circulation (Online)

Class Descriptors: **LC:** RC681.A1; **Dewey:** 616.105; **NLM:** W1 CI743

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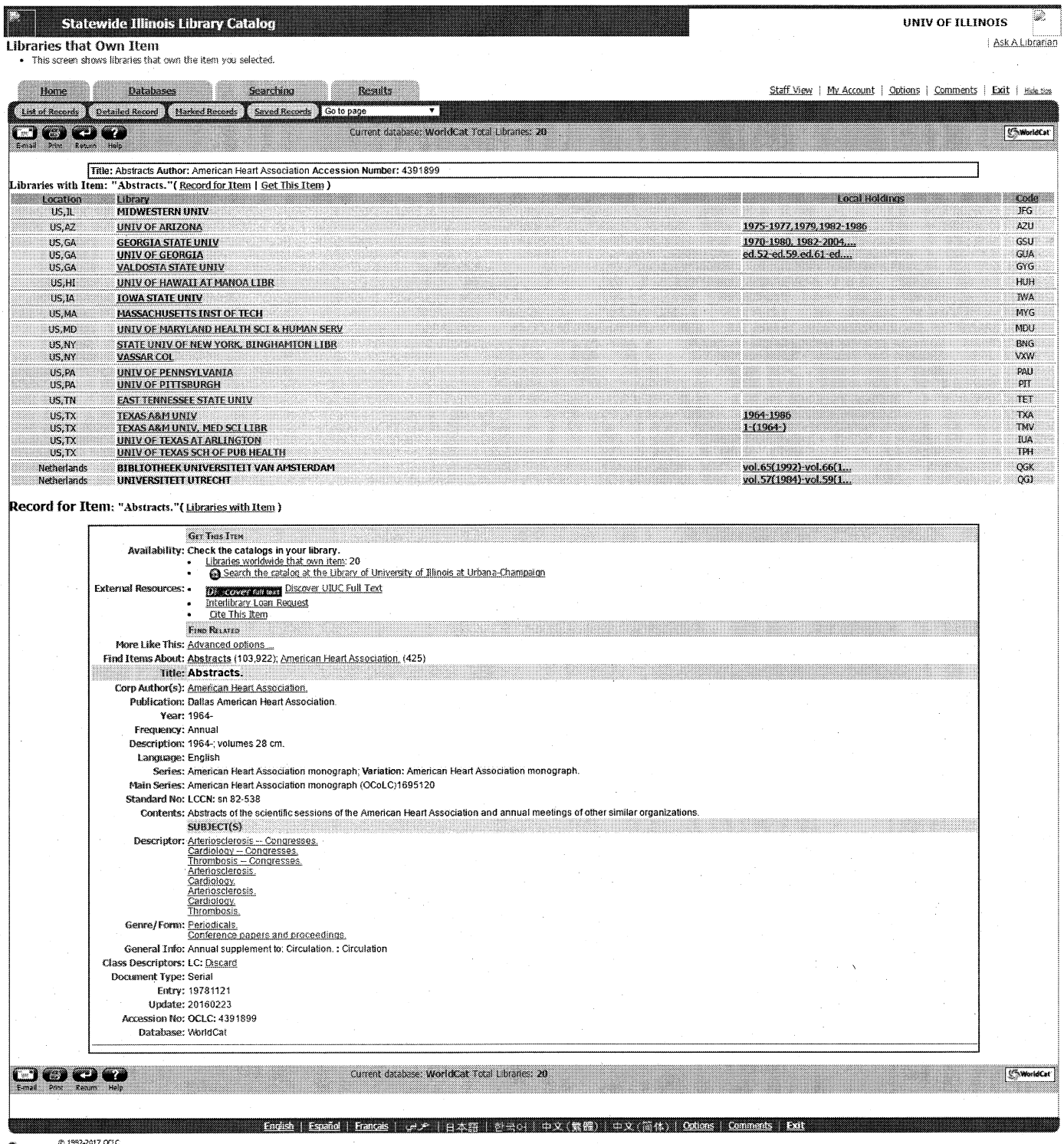

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Language: English

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Main Series: American Heart Association monograph (OCoLC)1695120

Standard No: LCCN: sn 82-538

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Voswinckel, R., et al. "Inhaled treprostinil sodium (TRE) for the treatment of pulmonary hypertension." Circulation. Vol. 110. No. 17. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA: LIPPINCOTT WILLIAMS & WILKINS, 2004.
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Abstracts From the Scientific Sessions 2004

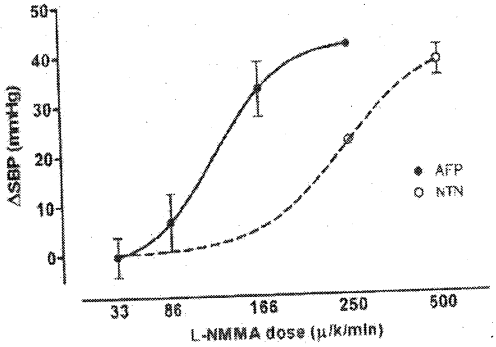
of membranous RhoA and phosphorylated ERM in brainstem were greater both in angiotensin II-treated rats and SHR than in WKY. Valsartan reduced the expression levels of membranous RhoA in angiotensin II-treated rats and SHR. In addition, Y-27632 or valsartan reduced the expression levels of phosphorylated ERM in both groups. Subcutaneous infusion of phenylephrine increased SBP to the same level of angiotensin II infusion in WKY. However, it did not alter the expression levels of membranous RhoA and phosphorylated ERM. Conclusions: These results suggest that 1) the pressor response induced by central infusion of angiotensin II is substantially mediated by activation of Rho/Rho-kinase pathway in brainstem via AT1 receptors, 2) this pathway may also be involved in hypertensive mechanism in SHR.

1412

Endothelial Nitric Oxide and Hypertension in Autonomic Failure

Alfredo Gamboa, Cyndya Shibao, Andre Diedrich, Bonnie K Black, Ginnie Farley, Satish R Raj, David Robertson, Italo Biaggioni; Vanderbilt Univ, Nashville, TN

More than half of patients with autonomic failure (AF) have severe supine hypertension despite low or unresponsive norepinephrine levels and often undetectable plasma renin activity. Supine hypertension is related to increased vascular resistance but the mechanism is not known. To test the hypothesis that nitric oxide deficiency contributes to supine hypertension we blocked endogenous nitric oxide synthase with L-NMMA in 5 AF patients and 7 normal controls (supine SBP 173±6 and 107±5 mmHg, respectively). Systolic blood pressure (SBP) was normalized to 110 mmHg in AF with graded head-up tilt, and baroreflexes were eliminated with trimethaphan in normal controls to mimic autonomic failure. The pressor response to graded doses of L-NMMA was shifted to the left in AF (Figure); The dose necessary to increase SBP by 30 mmHg was 3.4-fold lower in AF compared to controls (136±24 and 465±103 μg/k/min respectively, p<0.02). In conclusion, contrary to our original hypothesis, our results suggest an increased tonic release of nitric oxide in AF. Thus, NO deficiency does not contribute to supine hypertension in autonomic failure. On the contrary, this enhanced tonic NO may contribute to orthostatic hypotension in these patients.



1413

Oral Administration of a Mineralocorticoid Receptor Antagonist Reduces Brain, Heart, and Blood-borne Proinflammatory Cytokines in Heart Failure

Yu-Ming Kang, Carver College of Med, Univ of Iowa, Iowa City, IA; Ralph F Johnson, Univ of Iowa, Iowa City, IA; Zhi-Hua Zhang, Carver College of Med, Univ of Iowa, Iowa City, IA; Robert M Weiss, Carver College of Med, Univ of Iowa and VA Med Ctr, Iowa City, IA; Alan K Johnson, Univ of Iowa, Iowa City, IA; Robert B Felder, Carver College of Med, Univ of Iowa and VA Med Ctr, Iowa City, IA

Introduction: Brain and blood-borne cytokines may contribute to neurohumoral excitation in heart failure (HF). We previously reported that blockade of mineralocorticoid receptors (MR) in the central nervous system with spironolactone (SL) reduces circulating tumor necrosis factor (TNF)-α in HF rats. The effect of SL on proinflammatory cytokines (PIC) in the brain and on other important circulating PIC - interleukin (IL)-1β and IL-6 - was not determined. **Hypothesis:** Chronic treatment with oral SL will reduce brain and blood-borne PIC in rats with HF following MI. **Methods and Results:** Rats underwent coronary artery ligation to induce MI (48.2±2.0% of left ventricle, with ejection fraction of 35.5±4.1% by echocardiography), or sham surgery (SHAM). Six weeks later, immunohistochemistry of the paraventricular nucleus (PVN) of hypothalamus, a region critical to cardiovascular regulation, revealed more PVN neurons (MI vs SHAM, **P<0.01) positive for TNF-α (59.5±3.3** vs 10.8±0.9) and IL-1β (70.7±3.9** vs 13.8±1.2) in MI (n=6) than in SHAM (n=6) rats. Double staining demonstrated that these neurons were distributed among PVN neurons expressing Fra-like immunoreactivity, indicating chronic neuronal activation. MI rats (n=6) treated with SL (1 mg/kg/day orally for 6 weeks) had fewer (MI+SL vs MI, #P<0.01) Fra-like positive PVN neurons (85.5±5.4# vs 183.8±5.0), and fewer PVN neurons positive for TNF-α (22.4±1.8%# vs 32.4±1.7%) and IL-1β (19.1±1.3%# vs 38.4±2.1%). Levels of TNF-α, IL-1β and IL-6 in brain and heart tissues and in plasma were also lower in MI rats treated with SL (see table). **Conclusion:** In rats with ischemia-induced heart failure, orally administered SL has a global inhibitory influence on the appearance of proinflammatory cytokines in brain, heart and plasma. The beneficial influence of MR antagonism in patients with HF may result at least in part from blocking aldosterone-induced cytokine synthesis. (Table: *P<0.05 MI+SL vs MI+VEH)

Group	plasma IL-1β (pg/ml)	plasma IL-6 (pg/ml)	heart IL-1β (pg/mg protein)	hypothalamus IL-1β (pg/mg protein)	hypothalamus TNF-α (pg/mg protein)	brain stem IL-6 (pg/mg protein)	brain stem TNF-α (pg/mg protein)	cortex IL-1β (pg/mg protein)	heart BW Ratio (mg/g)	lung/BW Ratio (mg/g)
MI+VEH (n=7)	131.1±10.9	119.5±9.7	58.4±6.5	47.1±7.5	6.8±0.7	8.1±0.9	37.1±10.1	26.4±4.1	7.9±0.2	13.5±0.6
MI+SL (n=7)	57.5±3.1*	63.2±6.6*	32.6±5.9*	29.4±5.1*	3.8±0.6*	2.8±0.5*	39.4±5.5*	25.8±5.2	5.4±0.3*	12.1±0.6*
SHAM+SL (n=6)	48.3±3.6	53.7±2.8	23.7±6.5	17.4±4.9	2.8±0.7	2.1±0.6	25.3±4.8	24.5±4.9	3.9±0.1	9.2±0.3
SHAM+VEH (n=6)	53.8±2.4	58.1±2.6	27.6±5.4	16.8±4.9	3.2±0.9	2.4±0.8	28.0±8.7	23.6±6.5	3.4±0.1	9.1±0.3

Pulmonary Arterial Hypertension: New Therapies

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Abstracts 1414–1418

1414

Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension

Robert Voswinckel, Beate Enke, Andre Kreckel, Frank Reichenberger, Stefanie Krick, Henning Gall, Tobias Gessler, Thomas Schmehl, Markus G Kohstall, Friedrich Grimminger, Hossein A Ghofrani, Werner Seeger, Horst Olschewski; Univ Hosp Giessen, Giessen, Germany

Objective: To evaluate the effects of inhaled TRE on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension (PH) and to assess safety, tolerability and clinical efficacy in patients with severe PH. **Background:** TRE is a stable prostacyclin analogue that has been approved for treatment of pulmonary arterial hypertension as a continuous subcutaneous infusion. Iloprost, another prostacyclin analogue, has been shown to be efficacious in a randomised controlled study as repetitive inhalation. **Methods**: In an open-label study a preservative free solution of inhaled TRE was applied to 17 patients with severe pulmonary hypertension during Swan-Ganz catheter investigation. Patients received a TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 μg/ml). Hemodynamics were observed for 2 hours. Two patients with idiopathic PAH received compassionate treatment with 4 inhalations of TRE per day after the acute test. **Results**: Patients (male/female = 4/13) suffered from iPAH (n=5), PAH other (n=8) and CTEPH (n=4); PVR 948 ± 112 dyn*s*cm^{-5}, PAP 48.3 ± 2.7 mmHg, PAWP 8.9 ± 0.5 mmHg, CVP 10.8 ± 1.6 mmHg, CO 3.8 ± 0.3 l/min, SvO2 61.8 ± 1.8 %. TRE inhalation resulted in a sustained, highly pulmonary selective vasodilatation over 120 minutes. Maximum PVR decrease was -31.2 ± 4.5 % after 30 min. PVR and SVR at 120 minutes after inhalation were 89.2 ± 4.2 % and 101.0 ± 4.0 % of the baseline values, respectively. The AUC for the observation period (120min) was -22.9 ± 3.8 % for PVR and -4.9 ± 3.2% for SVR. The compassionate use patients have been treated for more than 3 months. In both patients NYHA class improved (from IV to III and from III to II), and six minute walk increased (from 0 m (bedridden) to 143 m, and from 310 m to 486 m, respectively). No side effects have been observed by the patients during long-term treatment. **Conclusion:** Inhaled TRE shows strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing. Tolerability is excellent even at high drug concentrations and short inhalation times (3 breaths). Long-term treatment effects are very promising. The current results warrant controlled studies investigating this approach in a larger series of patients. Supported by Lung RX

1415

Rho-kinase in Pulmonary Hypertension

Ken Ishikura, Norikazu Yamada, Akihiro Tsuji, Satoshi Ota, Mashio Nakamura, Masaaki Ito, Naoki Isaka, Takeshi Nakano; Mie Univ Sch of Med, Tsu, Japan

Objectives: Pulmonary hypertension (PH) is a poor prognostic disease with limited treatment. Rho-kinase is involved in the pathophysiology of several diseases underlying smooth muscle hypercontraction. But the role of is unknown. The purpose of this preliminary report was to indicate the efficacy of fasudil, a Rho-kinase inhibitor in patients with pulmonary hypertension using interventional hemodynamic assessment. Methods: Fasudil was intravenously injected in 10 patients (9 female, mean ± SD, 46 ± 15 years, NYHA II n=2, III n=7, IV n=1) with primary (n=5) and secondary (n=5) PH who were not received any vasodilator. Fasudil was administrated 30mg with 1mg/min. Hemodynamic data were measured using Swan-Ganz catheter until 60 minutes after starting administration of fasudil. Hemodynamic and arterial blood gas data of baseline and the lowest total pulmonary resistance (TPR) time were compared. Results: The lowest TPR time was within 30 to 60 minutes after administration. Administration of fasudil significantly decreased TPR from 13.6 ± 6.8 U to 10.3 ± 4.9 U (-23.2 ± 9.2 %, p < 0.001) and mean pulmonary arterial pressure (mPAP) from 43.6 ± 14.5 mmHg to 38.8 ± 13.9 mmHg (-11.6 ± 10.4 %, p < 0.02). Cardiac index (CI) was significantly increased from 2.39 ± 0.66 L/min/m^2 to 2.74 ± 0.73 L/min/m^2 (+16.5 ± 15.1 %, p < 0.01). Although TPR was equally decreased in both primary and secondary PH, the changes in the parameters that prescribed TPR, namely CI and mPAP, were different between the two groups subjects. Increased CI was a major factor into reducing TPR in primary PH, while reduced mPAP

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Expert Review of Cardiovascular Therapy
Volume 3, Issue 2, March 2005, Pages 347-360

Medical therapeutics for pulmonary arterial hypertension: From basic science and clinical trial design to evidence-based medicine (Review)

Sulica, R.[a], Poon, M.[b]

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[b]Mount Sinai School of Medicine, Department of Cardiology, Cabrini Medical Center, New York, NY 10003, United States

Abstract

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Pulmonary arterial hypertension is a severe disease with poor prognosis, caused by obliteration of the pulmonary vasculature as a result of pulmonary-vascular remodeling, active vasoconstriction and in situ thrombosis. Left untreated, pulmonary arterial hypertention results in right-ventricular failure and death. There has been dramatic progress in the treatment of pulmonary arterial hypertention during recent years. A remarkable number of randomized-controlled trials with agents know to target specific abnormalities present in pulmonary arterial hypertention have been completed. Most commonly, therapeutic efficacy was judged by the ability of the drug under study to improve exercise capacity and to decrease the rate of severe complications. Completed clinical trials have mainly evaluated patients with relatively advanced disease. Despite these advances, responses to therapy in pulmonary arterial hypertension are not uniformly favorable and frequently incomplete. In addition, the methods of delivery and the adverse effect profile of the currently available pulmonary arterial hypertension-specific drugs create further management difficulties. Based on newly identified pathobiologic abnormalities in the pulmonary vasculature, future studies are likely to focus on the discovery of new therapeutic targets. Clinical trial design will continue to evolve in an attempt to enable inclusion of patients with less advanced disease and evaluation of treatment combinations or comparisons of the currently approved drugs. © 2005 Future Drugs Ltd.

Author keywords

Ambrisentan, Bosentan, Epoprostenol, Exercise capacity, Hemodynamics, Iloprost, Pulmonary arterial hypertension, Sildenafil, Sitaxsentan, Treprostinil

Indexed keywords

EMTREE drug terms: adenosine, adrenomedullin, ambrisentan, anticoagulant agent, arginine, beraprost, bone morphogenetic protein, bosentan, calcium channel blocking agent, citalopram, endothelin A receptor, endothelin A receptor antagonist, endothelin B receptor, fluoxetine, hydroxymethylglutaryl coenzyme A reductase inhibitor, iloprost, metalloproteinase inhibitor, nitric oxide, potassium channel stimulating agent, prostacyclin, serotonin antagonist, sildenafil, simvastatin, sitaxsentan, unindexed drug, uniprost, vasculotropin, vasoactive intestinal polypeptide, vasodilator agent, warfarin

EMTREE medical terms: cell based gene therapy, clinical trial, death, disease course, disease severity, drug approval, drug dose regimen, drug efficacy, drug half life, drug safety, evidence based medicine, heart right ventricle failure, human, injection pain, injection site reaction, lung blood vessel, nonhuman, pathogenesis, prognosis, pulmonary hypertension, randomization, review, sepsis, thrombosis, treatment outcome, vasoconstriction

MeSH: Clinical Trials, Evidence-Based Medicine, Humans, Hypertension, Pulmonary, Research Design

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adenosine, 58-61-7; adrenomedullin, 148498-78-6; ambrisentan, 177036-94-1; arginine, 1119-34-2, 15595-35-4, 7004-12-8, 74-79-3; beraprost, 88430-50-6, 88475-69-8; bosentan, 147536-97-8, 157212-55-0; citalopram, 59729-33-8; fluoxetine, 54910-89-3, 56296-78-7, 59333-67-4; iloprost, 78919-13-8, 82889-99-4; nitric oxide, 10102-43-9; prostacyclin, 35121-78-9, 61849-14-7; sildenafil, 139755-83-2; simvastatin, 79902-63-9; sitaxsentan, 184036-34-8, 210421-74-2; uniprost, 81846-19-7; vasculotropin, 127464-60-2; vasoactive intestinal polypeptide, 37221-79-7; warfarin, 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2

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