



Special article

25 Years of endothelin research: the next generation



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ARTICLE INFO

Article history:

Received 28 July 2014

Accepted 28 July 2014

Available online 15 August 2014

ABSTRACT

In the past three decades, endothelin and endothelin receptor antagonists have received great scientific and clinical interest, leading to the publication of more than 27,000 scientific articles since its discovery. The Thirteenth International Conference on Endothelin (ET-13) was held on September 8–11, 2013, at Tokyo Campus of the University of Tsukuba in Japan. Close to 300 scientists from 25 countries from around the world came to Tokyo to celebrate the anniversary of the discovery of the endothelin peptide discovered 25 years ago at the University of Tsukuba. This article summarizes some of the highlights of the conference, the anniversary celebration ceremony, and particularly the participation of next generation of endothelin researchers in endothelin science and the anniversary celebration. As a particular highlight, next generation endothelin researchers wrote a haiku (a traditional form of Japanese poetry originating from consisting of no more than three short verses and 27 *on*, or Japanese phonetic units) to describe the magic of endothelin science which they presented to the conference audience at the anniversary ceremony. The text of each haiku – both in its original language together with the English translation – is part of this article providing in an exemplary fashion how poetry can be bridged with science. Finally, we give an outlook towards the next 25 years of endothelin research.

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E.T. is coming home: Anniversary conference at the University of Tsukuba

In 1980, Robert Furchgott together with John Zawadzki published his observation that endothelial cells release a relaxing factor, a

discovery that ultimately would bring him the 1996 Lasker Award (Furchgott, 1996) and the 1998 Nobel Prize in Physiology or Medicine (Mitka, 1998; Williams, 1998). At the same time Hollywood director Steven Spielberg had started his work on “E.T., the Extraterrestrial”, a science fiction movie about a friendly alien lost on planet Earth, which

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has been named one of the 100 best movies ever made since 1923 by *Time* magazine (Corliss, 2011). In 1982, when “E.T.” hit the silver screen, de Mey and Vanhoutte’s work on the discovery of endothelium-dependent vasoconstriction was published (Barton, 2011; De Mey and Vanhoutte, 1982). Endothelial cell research towards the identification of the factor described by Furchgott virtually exploded shortly thereafter, but instead resulted in preliminary reports of the release of a peptidergic endothelial vasoconstrictor substance (Hickey et al., 1985; O’Brien et al., 1987; Rubanyi, 2011), the identity of which was finally unmasked within half a year of research work by Yanagisawa, Masaki, Goto and colleagues were at the University in Tsukuba, Japan, and gene and peptide sequences were disclosed in a paper published in *Nature* in 1988 (Yanagisawa et al., 1988b). Due to its endothelial cell origin, the peptidergic vasoconstrictor was named endothelin – abbreviated as “ET”, like the Hollywood movie. Ironically, in the movie the main character, a little boy named Elliot, says to ET: “You could be happy here [...] we could grow up together”. As it turns out, exactly this is what happened to many scientists who have embarked in endothelin research since it was discovered at the University of Tsukuba a quarter of a century ago and who in fact did grow up and spent their life with endothelin.

The Thirteenth International Conference on Endothelin (ET-13) was held on September 8–11, 2013, at Tokyo Campus of the University of Tsukuba (Emoto et al., 2014ab). On the occasion of the 25th anniversary of the discovery, close to 300 scientists from 25 countries from around the world came to Tokyo, where the conference was hosted by Chairs Professors Noriaki Emoto and Takashi Miyauchi. Honorary Conference Chairs were Professors Tomoh Masaki, Katsutoshi Goto, Paul M. Vanhoutte and Masashi Yanagisawa. Two years earlier, at the *Twelfth International Conference on Endothelin* (ET-12) in Cambridge, UK, the inaugural, *First Tomoh Masaki Award* had been presented to Professor Masashi Yanagisawa. He recently returned home to the University of Tsukuba, where he, in the 1980s, summarized the discovery of endothelin in his Ph.D. thesis as a graduate student of Professor Tomoh Masaki (Barton et al., 2012a). Work and contributions of researchers leading to the discovery of endothelin and its receptors have been published in previous articles (Barton et al., 2012a; Masaki, 1989, 1998, 2004; Masaki and Sawamura, 2006). To the great joy of the Conference Faculty, Professor Tomoh Masaki, who will be celebrating his 80th birthday in October 2014, was able to attend the ET-13 festivities (Fig. 1), and also enjoyed a chamber music concert performed by world-renowned musicians Dimitri and Vovka Ashkenazy prior to the Presidential Dinner (Fig. 3).



Fig. 1. 1: ET-13 Presidential Dinner Announcement board. 2 and 3: Professor Paul Vanhoutte and Professor Tomoh Masaki at the Presidential Dinner of the Thirteenth International Conference on Endothelin, held on September 9, 2013 at the Hotel Chinzanso Toyko. Photographs courtesy of Angus Hubbard, London, United Kingdom.

First generation endothelin scientist receives *The Second Tomoh Masaki Award*

At the Thirteenth International Conference on Endothelin, Professor Katsutoshi Goto was honored as the recipient of the *Second Tomoh Masaki Award* (Emoto et al., 2014b) (Fig. 2). Professor Goto, a pharmacologist by training, importantly contributed to the purification of endothelin, and also set up the *in vitro* assays using aortic ring preparations (Vane, 1990). In work led by Professor Masaki and Professor Yanagisawa and with the support of the biochemist Professor Sadao Kimura, Professor Goto's efforts also helped characterize the endothelin

peptide as a vasoactive substance in rats (Yanagisawa et al., 1988a). At the ET-13 conference, Professor Yanagisawa accepted the award on behalf of Professor Goto who was unable to attend the conference (Fig. 2). During the award ceremony, Professor Yanagisawa presented the audience with memories and historical anecdotes on working with Professor Goto as a graduate student in Professor Masaki's laboratory (Fig. 2). Professor Yanagisawa pointed out how crucial and instrumental Professor Goto's support had been in the process of the discovery of endothelin, again emphasizing the importance of good mentorship and clear scientific communication (Barton and Pollock, 2012; Emoto et al., 2014b).



Fig. 2. 1 through 3: Impressions from the Young Investigator Award Ceremony. 4 and 5: Presentation of *The Second Tomoh Masaki Award* to Professor Katsutoshi Goto by the ET-13 Conference Chairs. On behalf of the recipient Professor Goto who was unable to attend the conference and is shown on the slide in the background (5), Professor Masashi Yanagisawa accepts the award. All photographs courtesy of Suzette Sandin, Sherbrooke, Canada.

25 years later: The next generation of endothelin researchers

During the preparation for ET-13 and after the first conference abstracts had been submitted, the Conference Chairs realized that ET-13 was going to be the first endothelin conference to include presenters who were born *after* the discovery of endothelin (the final manuscript was submitted to *Nature* on December 1, 1987, and published March 30, 1988 (Yanagisawa et al., 1988b)). As a period of 25 years reflects a generation it became clear that these young scientists, aged 25 or less in 2013, indeed are the next generation of endothelin researchers (Fig. 4). The importance of promoting young scientists in the endothelin field (Figs. 2, 4, and 5) (and in biomedical research in general) has already been discussed in an article in Endothelin XII, the Proceedings of the previous endothelin conference (Barton et al., 2012b), by Professors Matthias Barton and David Pollock (Barton and Pollock, 2012).

Since it was discovered at the University of Tsukuba by graduate student Masashi Yanagisawa, who at the time was working under the mentorship of Professor Tomoh Masaki, endothelin has always been linked to Japan (Emoto et al., 2014b). Moreover, the ET-13 conference provided a chance to celebrate the discovery of endothelin at its birthplace, the University of Tsukuba, a quarter of a century later.

With the aim to further improve the visibility of the new generation (Figs. 2, 4, and 5), the ET-13 Conference Chairs, Professors Noriaki Emoto and Takashi Miyauchi, not only invited younger researchers to join the conference faculty, but also increased the number of Young Investigator Awards and Travel Grants to an unprecedented level (Emoto and Yanagisawa, 2014) (Figs. 3 and 5).

Young investigators have always been a key element of the international Endothelin Conferences, and this was also the case at ET-13 (Fig. 5). To further highlight their essential role in endothelin research (Barton and Pollock, 2012), Angus Hubbard (U.K.) presented to the Conference Chairs the idea to introduce - as a first for any Endothelin Conference - a new series of online-only interviews having a young researcher and an established investigator in the field of endothelin research discuss about endothelin and their career in science. This newly launched series was named "The Endothelin Talks" (Appendix A). Filmed and recorded on site at ET-13 in Tokyo, the first set of Endothelin Talks include discussions between Julia Straube (Germany) and Masashi Yanagisawa (Japan), between Rebecca Moorhouse (U.K.) and Paul M. Vanhoutte (Hong Kong), and between Meghana Pandit and Donald E. Kohan (both U.S.A.). The Endothelin Talks are being published with this article and are available online (Appendix A).



Fig. 3. 1: World-renowned musicians, Pianist Vovka Ashkenazy and Clarinetist Dimitri Ashkenazy, performing at the Presidential Dinner Concert on September 9, 2013, on the occasion of the 25th anniversary of the discovery of endothelin. 2: Professor Masashi Yanagisawa discusses music with the artists after standing ovations for the musicians for a wonderful performance. Photographs courtesy of Angus Hubbard, London, United Kingdom.



Fig. 4. The next generation of endothelin researchers. 1: Julia Straube, Germany responding to the questions of the audience after her oral presentation. 2: Rhéure Alves Moreira Lopes, Brazil, during the poster session. 3: Rebecca Moorhouse, (Edinburgh, U.K.). 4: Aiko Sonobe (Tsukuba, Japan) and Joseph Cacioppo (Urbana, IL, U.S.A.), with Professor Jennifer Pollock (Augusta, GA, U.S.A., now Alabama, AL, U.S.A.). 5: Raphael Wurm (Vienna, Austria), during his oral presentation 6: Joseph Cacioppo with Dr. Anthony Davenport (Cambridge, U.K.) at his poster. 7: Danielle Kamato (Melbourne, Australia), Rhéure Alves Moreira Lopes (Ribeirão Preto, Brazil, in the back) and Thomas Leurgans (Odense, Denmark, in light blue shirt), at the posters. 8 and 9: Louisane Desbiens (Sherbrooke, Canada) with Professor Jo de Mey (Odense, Denmark). 10: Danielle Kamato at the posters. 11: Professors Matthias Barton (Zurich, Switzerland) and Adviy Ergul (Augusta, GA, U.S.A.; ET-14 Conference Chair-elect), and Professor Masashi Yanagisawa (Tsukuba, Japan) at the celebration ceremony of the 25th anniversary of the discovery of endothelin. All photographs courtesy of Suzette Sandin, Sherbrooke, Canada.

Bridging poetry with science: A haiku about endothelin

As this was the 25th anniversary meeting, the Conference Chairs decided to showcase their youngest colleagues and their creative abilities unrelated to science at ET-13 during the ceremony of the anniversary celebration.

As one of the highlights of the celebration ceremony, the Conference Chairs launched a haiku (俳句) contest. A haiku is a traditional form of Japanese poetry originating from consisting of no more than three short verses and 27 *on*, or Japanese phonetic units. A haiku often poetically depicts a natural scenery and juxtaposes two images or ideas, which might at first sight sound opposite like the small and the immense, the near and the far away. Haikus are deeply rooted in the Japanese culture but are now acclaimed and used around the world. The idea of organizing a haiku contest came out quite naturally, since a haiku is characterized by its simplicity in the form and beautiful complexity in the meaning – just like endothelin might be.

Nine investigators under 25 years of age had submitted a research abstract which they presented at the conference and who were invited to participate in the contest. They all accepted and embraced the project

with great enthusiasm. In very personal ways, combining science with poetry, they described the history of endothelin research, the hopes the research in the field has created and – most of all – the work that remains to be done to further uncover the complexity of endothelin's biology. The vascular origin of endothelin was a theme in several of the haikus presented, and endothelin's multiple, non-vascular functions were presented as well. Most importantly, the young investigators in their haiku put the light on the global scale of today's research. At the same time, the human aspects reflected in some of these presentations confirmed once more that research on endothelin (often referred to as the “endothelin peptide family”) indeed resembles in many aspects a family the members of which enjoy coming together again every two years in a city from around the world to share discoveries and friendship.

At the Conference Dinner on September 10th, 2013, the next generation of endothelin researchers presented their scientific poetry to some members of the “first generation” of endothelin scientists with much humor and self-confidence (Figs. 6 and 7). As all contributions were outstanding, every contestant was named a winner.



Fig. 5. ET-13 Best Presentation Awards, co-sponsored by Elsevier Publishers, for the best oral presentation and best poster presentation. 1: Awardee Dr. Johannes Backs, Department of Cardiology Heidelberg University, Germany, during his presentation. 2: Awardee Dr. David Durgan, Department of Anesthesiology, Baylor College of Medicine, Houston, Texas, USA, at his poster. 3 and 4: The ET-13 Conference Chairs, Professors Noriaki Emoto and Takashi Miyauchi present the presentation awards to the award recipients. All photographs courtesy of Suzete Sandin, Sherbrooke, Canada.

The haikus of the winners (with their year of birth in parentheses) follow below, both in the original language, and their English translation. They might well be considered “birthday-gifts for its 25 birthday” to endothelin science:

Joseph Cacioppo (1989) The Department of Comparative Biosciences, University of Illinois at Urbana–Champaign, Urbana, IL, USA:

*"From cells derived, your
Name arises; many years
Since then have flown by.*

*Vessels contract, blood
Flow quickens. Function explored,
New purposes course.*

*Hearts draw inward, face
Increased pressure, solid their
Walls grow forever.*

*Cease compliance as
scars now thicken the green blue
threads beneath the skin."*

*"Once cleansing, kidneys
Falter, and spreading throughout
Now track toxins too.*

*Not unlike cousins
From serpents' fangs, your subtle
Rise can bring demise.*

*Yet also needed
As life begins for eggs to
Break surface within.*

*For new strands to twist
While hearts do loop, connecting
Each to the other."*

*"In early life you
Keep us warm, and hunger you
Hold at bay as well.*

*And lest all mice are
Spotted, all foals deaf, know your
Actions are heard wide.*

*As we glance back to
Glimpse the past, the future shines
Bright as scenes unfold.*

*Much to learn have we,
And much to teach do you, on
Life, all parts, so dear."*

Louisane Desbiens (1989) Department of Pharmacology, Université de Sherbrooke, Sherbrooke, Canada:

French original

*"Un accord subtil,
La chymase dans l'hiatus
Des endothélines"*

*"A subtle chord
Chymase in the cacophony
Of endothelins"*

Thomas Leurgans (1989) Department of Cardiovascular and Renal Research, the University of Southern Denmark, Odense, Denmark:

Dutch original

*"Familie van drie,
Tonen veel gelijkenis.
Toch zo verschillend"*

*"Family of three.
Look a lot like each other.
Yet so different"*

Rebecca Moorhouse (1988) Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK:

*"Sowing of a seed
branching in new directions
learning, year on year"*

Raphael Wurm (1989) Medical University of Vienna, Austria:

German original

*"Die Gefäße zu verstehen
Bedeutet
Allen Fluss zu begreifen"*

*"Understanding the vasculature
Means
Comprehending the flow of everything"*

Julia Straube (1990) Department of Pathology, University Hospital, Cologne, Germany:

German original

*"Gefäßzauberer,
25 Jahre, weiter suchend
Austausch von Nöten"*

*"Vascular wizard –
25 years, still lifting the fog
In need of a blog."*

Rhêure Alves Moreira Lopes (1988) University of São Paulo, Medical School of Ribeirão Preto, Brazil:

Portuguese original

*"Isso é minha sorte!
Conhecer o Japão.
Falar sobre endotelina"*

*"That's my good luck!
To meet Japan.
To talk about endothelin."*

Danielle Kamato (1990) Health Innovations Research Institute, RMIT University, Melbourne, Australia:

*"ET-1 opens
Amin Ion Channels
No its IP3"*

Aiko Sonobe (1990) University of Tsukuba, Tsukuba, Japan:

Japanese original

へ 世 二
ブ 界 十
夕 と 一
イ 駆
ド け
る

*"Twenty-one
Spreading around the globe
Peptide"*

One of the Conference Chairs-elect of the next endothelin meeting and Master of Ceremony of the Haiku contest (Figs. 6 and 7) surprised the Conference Chairs with a haiku which gives us a glimpse of the ET-14 conference to be held in 2015:

Adviye Ergul, Georgia Regents University, Augusta, Georgia, United States of America:

*"Pink azaleas bloom
Live oaks with Spanish moss shine
Savannah we meet"*



Fig. 6. Top panel: All generations of endothelin researchers have come together for the ceremony of the 25th anniversary of the discovery of endothelin (from left to right): Professor Pedro d'Orléans-Juste (Sherbrooke, Canada), Professor David Pollock (Augusta, GA, U.S.A. now Alabama, AL, U.S.A.; ET-14 Conference Chair-elect), Dr. Ariela Benigni (Bergamo, Italy), Dr. Anthony Davenport (Cambridge, U.K.), Professor Paul Vanhoutte (Hong Kong, China), Professor Takashi Miyauchi (Tsukuba, Japan), Professor Adviye Ergul, (Augusta, GA, U.S.A., wearing an original Japanese kimono and footwear; ET-14 Conference Chair-elect); Next generation endothelin researchers Danielle Kamato (Melbourne, Australia), Rebecca Moorhouse, (Edinburgh, U.K.), Joseph Cacioppo (Urbana, IL, U.S.A.), Thomas Leurgans (Odense, Denmark), Louisane Desbiens (Sherbrooke, Canada), Raphael Wurm (Vienna, Austria), Rhéure Alves Moreira Lopes (Ribeirão Preto, Brazil), Julia Straube (Köln, Germany), Professor Matthias Barton (Zürich, Switzerland), Professor Masashi Yanagisawa (Tsukuba, Japan), Professor Noriaki Emoto (Kobe, Japan), Professor Jun Yamashita (Kyoto, Japan), Professor Donald Kohan (Salt Lake City, UT, U.S.A.), and Professor David Webb (Edinburgh, U.K.). Professors Tomoh Masaki (Tokyo, Japan), and Katsutoshi Goto, (Tsukuba, Japan) were unable to attend the ceremony. Bottom left panel: The Haiku contestants in front of the typical, Japanese-style cartoon "Endothelin's 25th anniversary celebration" poster, with the "Masters of Ceremony", Professors Adviye Ergul and Matthias Barton, with Professor Yanagisawa. Bottom right panel: The ET-13 Conference Chairs Professors Takashi Miyauchi and Noriaki Emoto, celebrating and shown with the "Endothelin Birthday Cake". All photographs courtesy of Suzete Sandin, Sherbrooke, Canada.



Fig. 7. Haiku contest winners from all parts of the world: Danielle Kamato (Melbourne, Australia), Rebecca Moorhouse (Edinburgh, U.K.), Joseph Cacioppo (Urbana, IL, U.S.A.), Thomas Leurgans (Odense, Denmark), Louisane Desbiens (Urbana, Canada), Raphael Wurm (Vienna, Austria), Rhéure Alves Moreira Lopes (Ribeirão Preto, Brazil), and Julia Straube (Köln, Germany), shown with Professors Adviye Ergul (in an original Japanese kimono and footwear), Matthias Barton, and Masashi Yanagisawa. Photograph courtesy of Suzete Sandin, Sherbrooke, Canada.

New science presented at the University of Tsukuba, Tokyo Campus

Conference attendees presented work and lectures on clinical studies in nephrology, cardiology, internal medicine (Campia et al., 2014), oncology, dermatology, ophthalmology, as well as basic research, including physiology, biochemistry, pharmacology (Shimojo et al., 2014), and molecular biology. Potential applications of new endothelin receptor antagonists in parasitic diseases were discussed (Dai et al., 2012; Freeman et al., 2014), and clinical presentations addressed treatment of pulmonary arterial hypertension (Adachi et al., 2014) as well as hopes (Adlbrecht et al., 2014) and disappointments of clinical trials (Kohan et al., 2012; Reichetzedler et al., 2014).

Endothelin research – The next 25 years

After a quarter of a century, endothelin has reached all continents (Fig. 8), projects studying endothelin produced more than 27,000 research articles (Barton and Pollock, 2012), and pharmaceutical research resulted in the development of new, orally active drugs (Kohan et al., 2012), three of which are now available to physicians to treat patients with life-threatening diseases (Miyagawa and Emoto, 2014; Rubin, 2012; Tanabe et al., 2014). What began in 1988 with the isolation of the endothelin peptide from endothelial cells, followed by the discovery of its receptors shortly thereafter (reviewed in Barton and Yanagisawa, 2008), has resulted in a tremendous advancement of knowledge, both in basic science as well as in clinical medicine where new treatments for human disease are now available (Miyagawa and Emoto, 2014; Rubin, 2012; Tanabe et al., 2014). For more than ten years endothelin antagonists have been part of the therapeutic armamentarium of physicians treating pulmonary arterial hypertension (Miyagawa and Emoto, 2014; Rubin, 2012; Tanabe et al., 2014), and the development of new therapeutic targets continues (Kohan et al., 2012). We expect that within the next decades well-designed clinical studies using endothelin receptor antagonists at the right dose and in the right patients for the

right therapeutic indication might reveal a new way by which interfering with endothelin action may improve health and prolong lives (Barton et al., 2006; Kohan and Barton, in press; Kohan et al., 2012; Said et al., 2011; Said and Theodorescu, 2012; Schneider and Mann, 2014).

In 2011, the International Advisory Board of the International Conferences on Endothelin launched its website (Endothelins.com, 2011) with the goal to inform and educate patients, scientists, students, and laymen about endothelin as well as past and future endothelin conferences. The ET-12 Conference Chairs started the tradition to make video recordings of presentations delivered at the endothelin conferences and to provide access to these presentations, thereby creating a permanent record of the endothelin conferences (Barton et al., 2012b). This tradition that has been continued at ET-13, and all presentations are now available online (Media data base, 2012). Over the past two years, the presentation videos on the endothelin website has been accessed more than 60,000 times from over 100 countries around the world (Fig. 8), averaging currently about 100 visits per day, a number we expect to increase even further. We are much looking forward to the next conference to be held from September 2–5, 2014 in Savannah, Georgia, U.S.A. (ET-14, 2014). We wish the ET-14 Conference Chairs, Professors Adviyeg Ergul, David Pollock, and Anil Gulati, much success with their meeting and to again welcome and accompany the next generation of endothelin researchers to continue its scientific journey.

Acknowledgements

The authors thank Augus Hubbard London, and Suzete Sandin Sherbrooke, for filming and photography of ET-13 in Tokyo.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.lfs.2014.07.035>.

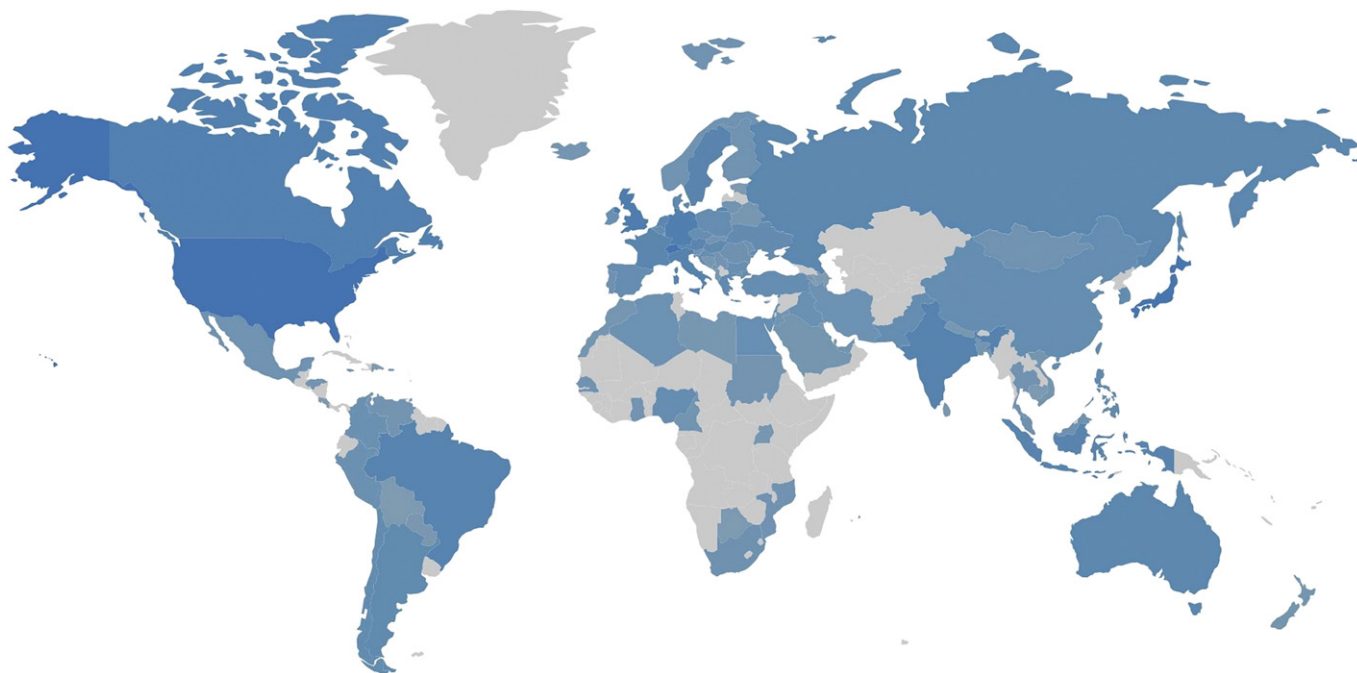


Fig. 8. Graphic summary of countries accessing lectures and presentations of the ET conferences on website endothelins.com between Spring 2012 and Spring 2014. In the past two years, the endothelin presentation videos have been watched more than 60,000 times in over 100 countries from around the globe. Color intensity reflects the frequency of page visits. Source: vimeo.com.

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