

Editorial

## Defining heart failure

R. Coronel<sup>a,\*</sup>, J.R. de Groot<sup>a</sup>, J.J. van Lieshout<sup>b</sup>  
On behalf of the editorial team of Cardiovascular Research

<sup>a</sup>*Taskforce for Heart Failure and Aging, Experimental and Molecular Cardiology Group, Department of Clinical and Experimental Cardiology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

<sup>b</sup>*Taskforce for Heart Failure and Aging, Department of Internal Medicine, Academic Medical Center, Meibergdreef 9, room M053, 1105 AZ Amsterdam, The Netherlands*

The definition of heart failure is hampered by the wide variability of the clinical symptoms and signs, and of their etiologies. Many attempts have been made to come up with a general set of criteria that describe heart failure [1–7]. These criteria include clinical, epidemiological, pathophysiological, and exercise-related criteria and criteria derived from the patient's response to therapy. The need for a more circumscribed definition reflects the hope to be able to stratify patient groups, to detect heart failure at an earlier stage and to optimally treat patients. At the basis of this need is our wish to understand heart failure as a pathogenetic entity. Moreover, to attain this purpose a clear definition is required for the design of adequate experimental protocols.

From medical history we know that the understanding of diseases often has started with the recognition of consistency in a set of symptoms and signs. The starting point for our knowledge therefore is the definition of such a set of characteristics. Here, pathophysiological and medical objectives may, however, lead to conflicts: those searching for a pathophysiologic entity may produce a common denominator of the characteristics, whereas those concerned with the optimal treatment of their patients may come up with a description that covers all possible appearances of the phenomenon. Debates between followers of the standpoint of comprehensiveness and those of brevity continue [4–7].

In order to uncover the dilemmas in the definition of heart failure, the editors of *Cardiovascular Research* have recently performed a survey amongst the Journal's reviewers. A letter was sent to 2238 active reviewers with a request for confirmation of data stored in the Journal's database. In the same letter the reviewers were asked to

give a definition of heart failure in less than 150 words. In the 2 months following the mailing 1018 responses were obtained, 130 of which included a definition of heart failure.

The editors' initiative was not welcomed by all. One reviewer reprimanded the editors stating that '*it is a major error for a journal to accept controversies concerning the definition of heart failure ...*'. Another reviewer reproved us for advancing dichotomy in science and medicine: '*Since Aristotle ... everything [is] to be cleaved into two possibilities: true or false, yes or no ... Nature has nowhere drawn such a line*'. A third reviewer declared that '*... basically, heart failure simply does not exist..[and] any attempt to define the clinical syndrome will lead to misconception of the etiologies ...*'. In spite of this we firmly believe that solutions are contained in controversies and that it is the obligation of science to expose them.

Many definitions of heart failure given by our reviewers shared components, but not a single definition was the same as another, with the exception of three cases where it was defined as '*failure of the heart*'. The references (six cases) to textbooks or the WHO that were received were also different. This lack of consensus and the low response rate to the mailed request probably reflects the difficulty of defining heart failure.

The definitions were classified as 'clinical' (inclusion of the word 'clinical', 'syndrome', 'disease', or when symptoms or signs were mentioned) and/or 'pathophysiological' (when causal relationships were identified, or mechanisms were mentioned). Seventy (54%) clinical and 102 (78%) pathophysiological definitions were counted, of which 48 were a combination of the two. Six responses could not be classified.

*Clinical definitions:* heart failure was considered a syndrome in 31 cases (44%) and a 'disease' ('state' or 'entity') in 10 (14%). Required symptoms were: dyspnea in 20, fatigue in 13, and their dependence on physical

\*Corresponding author. Tel.: +31-20-566-3267; fax: +31-20-697-5458.

E-mail address: r.coronel@amc.nl (R. Coronel).

activity in 19 definitions. Required clinical signs included: edema in 13, tachycardia in two, and rales in one definition. A low ejection fraction (EF) was considered the only criterion by one reviewer ('EF<43%'), and was included in the definitions by 13 others, although one reviewer called it an 'inadequate' and another a not obligatory feature for the definition. The systemic nature of heart failure was referred to in merely 15 cases. It was called progressive in 10, chronic in five and lethal in one. A form of subdivision of the definition was provided in 33 cases (left/right, forward/backward, systolic/diastolic, acute/chronic), however mostly without mention of criteria for subclassification.

Most (48/70) of the clinical definitions included a pathophysiological mechanism or cause–effect relation and the common denominator of these definitions were variants of the definitions by Braunwald [1,5] usually worded as: 'A clinical syndrome caused by the inability of the heart to supply blood to the tissues commensurate to the metabolic needs of that tissue'. Less than half of these (22/48) added to this: 'or only at the expense of elevated filling pressures' or phrases to the same effect.

*Pathophysiological definitions:* of the 102 'pathophysiological' definitions 68 included words indicating 'pump function', 66 included 'mismatch' or 'inadequate' and 50 words derived from 'metabolism', 'demand', or 'requirement'. Blood supply was mentioned in 28 cases. The word 'compensation' was present in 16 definitions. In merely 15 definitions pump function was subdivided in systolic and diastolic. Other definitions included neuro-hormonal effects (15), cardiac lesions (6), tissue architecture or extracellular matrix (5),  $\text{Ca}^{2+}$ -cycling (3), developmental origins (2), inflammation (1) and gene expression (1). Five definitions included etiologies (myocardial, valvular, etc). Two reviewers added to this that the cause should be other 'than the loss of body fluids or of vascular tone' thereby setting heart failure apart from acute circulatory failure.

Some definitions stand out for their originality or extensiveness. Dr. Klassen gave an extensive, combined clinical–pathophysiological definition emphasizing the role of the neurohumoral system, and underlined the reversibility of the 'destructive positive feedback' mechanisms. Stabilization and reversibility in all but its final stages of heart failure is also the theme in Dr. Power's definition to which a charge was added of 'obsession with single purpose therapy' of clinical medicine. Interestingly, Dr. De Tombe defined heart failure not as a state but rather as the moment in time 'when the heart becomes the rate limiting factor [for the circulation]'. Dr. Taegtmeier needed 10 words: 'A systemic disease that begins and ends with the heart'. Dr. Lakatta's contribution contained a hypothesis ('Localized inhomogeneity of  $\text{Ca}^{2+}$ -regulation') for three  $\text{Ca}^{2+}$ -related manifestations of heart failure.

More playful definitions were given by Dr. Spaan ('I

suspect it has something to do with spiraling down of myocardial perfusion reduction by decreased contraction and decreasing contraction by reduced perfusion') and Dr. Lineaweaver ('failure of systemic perfusion, compassion, or courage consequent to the default of the heart or one of its metaphorical functions').

*A clinical syndrome?* One of the controversies is whether heart failure should be considered a syndrome (a collection of symptoms). One reviewer mentioned that clinical symptoms or signs are not required at all, another definition read 'EF less than 43%'. On the other hand, a reviewer stated that '...signs plus or minus symptoms must also be present (i.e. low EF alone is not sufficient)'. The latter point of view was supported by the reviewer who wrote that '...asymptomatic patients with a depressed ejection fraction are NOT heart failure patients, while those with preserved ejection fraction but exertional dyspnea... are heart failure patients'. Whereas many would agree that the definition of heart failure is of no consequence because the syndrome is easily recognized and is a mere starting point for further diagnostics, the matter of defining heart failure carries some importance for cardiovascular research involved in pathophysiologic studies. If defined as a clinical syndrome with 'exertional dyspnea and fatigue', heart failure does not occur in experimental animals and can only be investigated in conscious humans. Moreover, isolated (human) hearts or myocytes cannot be characterized as 'failing'. Yet, it is important to design studies and experimental models that mimic the syndrome of heart failure, however defined, more closely in order to extrapolate results obtained in these model systems to the heart failure patient (and vice versa).

*Causality:* one contributor stated that heart failure is a 'final', another that it is the 'common' 'manifestation of almost any cardiac disorder'. Other reviewers supported this view ('regardless of pathology') or pointed to extracardiac causes of heart failure. When combined this would lead to the general statement that heart failure is the common final process of almost any cardiovascular disorder.

Dr. Doevendans wrote that the syndrome is 'primarily a circulatory insufficiency, with cardiac or extracardiac causes', a view that is shared in fact by all those who adopted a version of Braunwald's definition ('inability to supply blood to the tissues commensurate to the metabolic needs'). This was most unambiguously formulated by Dr. Warren as '[heart failure is] Generalized inadequate perfusion'. Dr. Freedman gave his view as a physiologist describing 'the inability to meet the oxygen consumption needs of vital organs (including the heart itself)'.

Heart failure considered as the final common process of a plethora of cardiac and extracardiac diseases, therefore, should be defined according to its consequences rather than to its etiologies. If one accepts that the balance between oxygen delivery to and oxygen requirement of the tissues

is the common characteristic (not the cause!) of heart failure one may wonder why not measures of peripheral tissue perfusion/oxygenation have been implicated in the assessment of (the degree of) heart failure or in its definition. Given the constancy of arterial O<sub>2</sub> content, the tissue O<sub>2</sub> is predominantly a function of arterial blood flow [8]. It can be expected that peripheral tissue perfusion fails before blood pressure(s) is (are) affected because blood pressure is a strongly regulated systemic parameter, which latter point was underscored by Drs. Duncker and Verdouw. In heart failure patients, cardiac output is a difficult parameter to monitor and plays a subservient role to arterial blood pressure. Peripheral tissue oxygenation therefore may provide a parameter that helps bridge the gap between the clinical and pathophysiological approach to heart failure. In addition, it may help aligning the various definitions of heart failure relative to a common measure.

Thus, within a group of scientists dedicated to cardiovascular research, consensus regarding the definition of heart failure is lacking, even between those that defined heart failure in the same category (clinical/pathophysiological). In addition, there is disagreement about the criteria for heart failure. We acknowledge the input of Dr. Eckardt who effectively summarizes all of the above by writing that *'heart failure is the label for a cardiovascular syndrome that is lacking uniform criteria for definition'* and who subsequently defined heart failure from various standpoints (of the patient, clinician, researcher). Indeed, definitions in general and of heart failure in particular depend on the contexts in which the terms are used [6]. Clinical and experimental cardiovascular research of heart failure is in need of a definition of heart failure used in the same context.

## Acknowledgements

Dr. T. Opthof is gratefully acknowledged for critical reading of the manuscript. We thank the following reviewers of Cardiovascular Research for their contributions: Dr. R.F. Appleyard (USA), Dr. Junichi Araki (Japan), Prof. Makoto Arita (Japan), Dr. John Andrew Armour (Canada), Dr. Mike Artman (USA), Dr. Matthias Barton (Switzerland), Prof. Dr. Bernhard F. Becker (Germany), Dr. David Bohr (USA), Dr. Marvin O. Boluyt (USA), Dr. Mathias M. Borst (Germany), Dr. A. Brady (UK), Dr. Bodo Brandts (Germany), Prof. Dr. Günter Breithardt (Germany), Dr. Serge Brimiouille (Belgium), Dr. J. Bronzwaer (The Netherlands), Prof. Terrence J. Campbell (Australia), Prof. A. Capucci (Italy), Dr. Antonio Cevese (Italy), Dr. Francesco Cipollone (Italy), Dr. Edward B. Clark (USA), Prof. John G.F. Cleland (UK), Dr. Simon J. Conway (USA), Dr. Francisco G. Cosio (Spain), Prof. Dr. Peter W. de Leeuw (The Netherlands), Dr. Michel De Lorgeril (France), Dr. Pieter P. De Tombe (USA), Dr. László Dézsi (Hungary),

Dr. Pieter A. Doevendans (The Netherlands), Dr. Dirk J. Duncker (The Netherlands), Dr. Lars Eckardt (Germany), Dr. Robert Engler (USA), Prof. Erland Erdmann (Germany), Prof. Leif Erhardt (Sweden), Dr. E.L. Fallen (Canada), Dr. Giora Z. Feuerstein (USA), Dr. Jeffrey C. Freedman (USA), Prof. Manuel Galinanes (UK), Dr. Jan F.C. Glatz (The Netherlands), Dr. Lino M. Gonçalves (Portugal), Dr. Yoichi Goto (Japan), Dr. Stephen Greenwald (UK), Prof. Dr. R. Griebenow (Germany), Dr. Finn Gustafsson (Denmark), Dr. Sian E. Harding (UK), Prof. George Hart (UK), Dr. Jia-Qiang He (USA), Dr. Helge Hohage (Germany), Dr. Nico Hoogerwerf (The Netherlands), Dr. Magda Horackova (Canada), Dr. Ralph Houston (The Netherlands), Dr. Chikao Ibuki (Japan), Dr. M. Ideishi (Japan), Dr. Arnfinn Ilebekk (Norway), Dr. Hiroyuki Ito (Japan), Dr. Andrew F. James (UK), Dr. Paul M.L. Janssen (USA), Dr. Ben Janssen (The Netherlands), Dr. Gareth W. John (France), Dr. Race L. Kao (USA), Prof. Elieser Kaplinsky (Israel), Dr. Bruce H. KenKnight (USA), Dr. David Kilpatrick (Australia), Dr. Gerald A. Klassen (Canada), Dr. Alexandros C. Kralios (USA), Dr. Stephen M. Krause (USA), Dr. L. Kuo (USA), Dr. Teresa Kus (Canada), Dr. Edward G. Lakatta (USA), Prof. Jacques Lenfant (France), Dr. René Lerch (Switzerland), Prof. Dr. Marcel Levi (The Netherlands), Dr. Jo Ann Lindenfeld (USA), Dr. William C. Lineaweaver (USA), Dr. Gianni Losano (Italy), Dr. Marie-Reine Losser (Canada), Dr. Jonathan C. Makielski (USA), Dr. Robert T. Mallet (USA), Dr. Jose Marin-Garcia (USA), Prof. James D. Marsh (USA), Dr. Richard McCabe (USA), Prof. John J.V. McMurray (UK), Dr. György Nádasy (Hungary), Dr. Benno Nafz (Germany), Dr. Stanley Nattel (Canada), Dr. Robin M. Norris (UK), Dr. Brian Olshansky (USA), Prof. Lionel H. Opie (South Africa), Dr. Mary Osbakken (USA), Dr. C. Subah Packer (USA), Dr. Pasquale Pagliaro (Italy), Dr. Jaideep Pandit (UK), Dr. Ioannis A. Paraskevaidis (Greece), Dr. GianFranco Parati (Italy), Dr. Ron J.G. Peters (The Netherlands), Dr. J. Thomas Peterson (USA), Dr. Burkert Pieske (Germany), Dr. Yigal M. Pinto (The Netherlands), Prof. Hans Michael Piper (Germany), Dr. John M. Power (Australia), Prof. Dr. Jan H. Ravesloot (The Netherlands), Prof. Nina Rehnqvist-Ahlberg (Sweden), Dr. James F. Riordan (USA), Prof. Fred D. Romano (USA), Dr. Stuart D. Rosen (UK), Prof. Urs T. Rugg (Switzerland), Dr. Tetsunori Saikawa (Japan), Dr. Tohru Sawanobori (Japan), Dr. V. Schachinger (Germany), Prof. Marcus Schaub (Switzerland), Dr. Regien G. Schoemaker (The Netherlands), Dr. Bodo Schwartzkopff (Germany), Dr. Robert H.G. Schwinger (Germany), Dr. Michael J. Shattock (UK), Prof. Maarten L. Simoons (The Netherlands), Dr. Donald R.J. Singer (UK), Prof. Jos A.E. Spaan (The Netherlands), Dr. Richard Sutton (UK), Dr. Johan P. Suyderhoud (USA), Dr. B. Swynghedauw (France), Dr. Heinrich Taegtmeier (USA), Prof. Dr. Arnoud van der Laarse (The Netherlands), Prof. Daya R. Varma (Canada), Dr. S. Cora Verduyn (Spain), Dr. Adriaan

A. Voors (The Netherlands), Dr. Håkan Wåhlander (Sweden), Dr. Jeremy P.T. Ward (UK), Dr. John B. Warren (UK), Dr. Raymond L. Woosley (USA).

## References

- [1] Braunwald E. Heart disease. A textbook of cardiovascular medicine, Philadelphia: WB Saunders, 1997.
- [2] Tavazzi L. Towards a more precise definition of heart failure. *Eur Heart J* 2001;22:194–195.
- [3] Adams KF, Zannad F. Clinical definition and epidemiology of advanced heart failure. *Am Heart J* 1998;135:S204–S215.
- [4] Poole-Wilson PA, Purcell IF. Letter to the editor. *Eur J Heart Failure* 1999;1:434.
- [5] Braunwald E. Comment by E. Braunwald. *Eur Heart J* 1983;4:447.
- [6] Julian DG. Editor's comment. *Eur Heart J* 1983;4:446.
- [7] Denolin H, Kuhn H, Krayenbuehl HP et al. The definition of heart failure. *Eur Heart J* 1983;4:445–448.
- [8] Harms MPM, Colier WNJM, Wieling W et al. Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. *Stroke* 2000;31:1608–1614.