(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(54) **Title:** METHOD AND DEVICE FOR THE DIAGNOSIS AND THERAPY OF CHRONIC HEART FAILURE
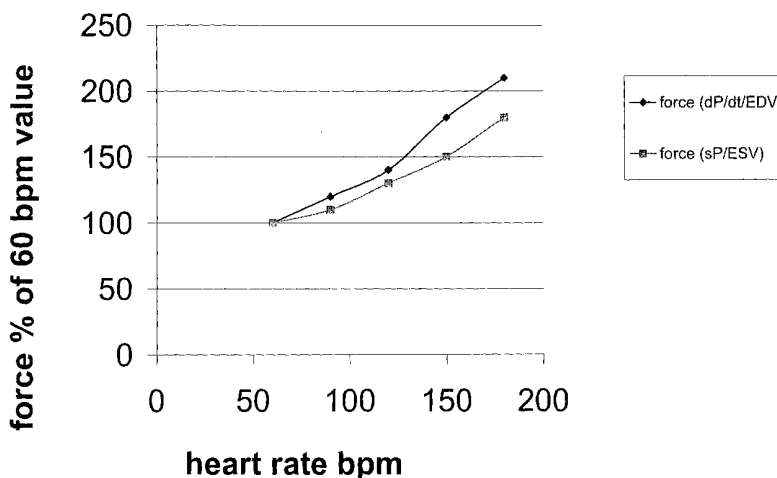
(57) **Abstract:** Method and device for the diagnosis and therapy of chronic heart failure comprising continuous monitoring of the patient and continuous determination of significant decompensation parameters during a sample period of normal patient life, recording the data determined, continuously monitoring these data during therapy, comparing the memorized data with those determined during the same time span of the sample period and comparing the duration of periods in which decompensation is present with the total duration of those periods during which decompensation is absent or conforms to that determined during the sample period.

DESCRIPTION

METHOD AND DEVICE FOR THE DIAGNOSIS AND THERAPY OF

CHRONIC HEART FAILURE

5

TECHNICAL FIELD

The invention relates generally to a method and the relative apparatus for

monitoring the physiological conditions of a patient, with particular reference to

cardiovascular function in the presence of chronic heart failure.

10   In particular the invention comprises a device incorporating a microprocessor, a

memory and a system for monitoring the ventricular function, from which certain

diagnostic information and the relative therapeutic options may derive.

The ventricular function is monitored together with the heart rate to establish the

individual force-frequency relationship of the patient. In the following the terms

15   heart rate and heart frequency have the same meaning.

BACKGROUND ART

An increased heart rate progressively increases the contractile force of the heart

(Bowditch phenomenon). In this respect, in a normal heart the influx of calcium

20   through the calcium channels is normally increased by high heart rate.

In humans, an increase in heart rate from 60 to 170 beats per minute stimulates

developed force.

When the heart rate exceeds 170 beats per minute, the force developed by the

ventricle begins to decrease.

If chronic heart failure and/or myopathic, valvulopathic or ischemic

cardiomyopathy is present, this intrinsic property of the myocardium is partially

or totally depressed, because of which the contractile force decreases for cardiac

frequencies of the order of 100 bpm or even lower. The decompensated

5   myocardium undergoes a phenotypic change with activity alteration of the

enzymes which regulate calcium homeostasis: diastolic uptake and systolic

release of calcium decrease and contractile performance improves only with

bradycardia.

The heart rate starting from which the contractile force begins to decline

10   diminishes progressively for known pathologies such as ischemic

cardiomyopathy, diabetic cardiomyopathy, mitral regurgitation and dilated

cardiomyopathy.

The optimum contraction rate, i.e. the rate corresponding to the strongest

contractile force, varies for each pathology, for each different stage of the illness,

15   and for each patient.

In these pathologies a decrease in the capacity of the ventricles to adapt to the

greater requirement occurs, this decrease sometimes being defined as loss of

ventricular pumping reserve; the contractile reserve loss is unable to support the

increase in the function requirement which occurs during exercise.

20   It therefore happens that when pathologies are present, a compensated system, in

which the greater function requirement is satisfied naturally by a positive force-

frequency relationship, passes to a decompensated or unstable system, in which

the force-frequency relationship is depressed, flattened or negative, i.e. the system

3

responds to a disturbing event by amplifying the effect of the disturbance, and

hence becomes unstable.

The deterioration and the possible inversion of the myocardial force-frequency

relationship is a mechanism of conversion from a compensation situation to a

5   cardiac decompensation situation in a diseased heart.

In advanced conditions of chronic heart failure the peak of the force-frequency

relationship is sufficiently displaced towards low frequencies to produce a

flattened or a negative slope on the rate spectrum between 80 and 160 beats per

minute (bpm), which in practice is the entire spectrum of the chronic heart failure

10   patient. This decrease in force as soon as the heart rate increases means that a

sudden rate increase predisposes the ventricles to dilation because of venous

overloading with increase in telediastolic pressure. Different therapies are known

for remedying chronic heart failure, aimed at reducing heart rate to remedy the

decrease in force with increase in rate, however the response of the individual

15   therapies must be adapted to the particular conditions of the patient.

For example, therapy with beta blockers has proved effective in cardiomegaly

regression and in improving the myocardial function in patients suffering from

dilated cardiomyopathy, however patients do not respond uniformly to this

therapy.

20   Because of the pejorative effect of inversion of the force-frequency relationship,

one of the effectiveness components of therapy with beta blockers derives from

the reduction in heart rate in itself.

4

If the bradycardia is sufficient to reposition the spectrum of heart operative

frequencies to sufficiently low levels, the negative part of the force-frequency

relationship is avoided.

The bradycardic action of beta blockers reduces the number of daily working

5   phases of the heart in the negative part of the force-frequency relationship.

As the flattening and the descending limb of the force-frequency curve appears at

different frequencies in the different types of cardiac decompensation and in

different patients, the effectiveness of the action of beta blockers is variable.

To optimize chronic heart failure therapy, it therefore appears essential to identify

10   in each patient the ascending part of the force-frequency curve and the specific

rate which when exceeded initiates the flattening and the descending part, in order

to optimize individual therapy for chronic heart failure.

The subsequent therapeutic action in an individual patient will be more

advantageous the closer the negative part of the force-frequency curve lies to the

15   basal heart rate.

DISCLOSURE OF THE INVENTION

The present invention generally concerns a method and relative apparatus for

determining the force-frequency relationship of an individual for the purpose of

20   recognizing and/or avoiding chronic heart failure.

The force-frequency relationship regions are initially identified to define the

normality and abnormality components of an individual patient.

These regions automatically change in response to a decompensation phase or the

absence thereof. The normality and abnormality limits of the force-frequency

relationship adapt specifically to the physiological and cardiological conditions of

the individual patient.

When a decompensation phase occurs, the sequence which led to the

decompensation phase is memorized.

5   The force-frequency relationship is then compared with the sequence which led to

the decompensation phase to anticipate its reoccurrence.

The invention provides a system comprising a microprocessor which from the

heart receives informative signals concerning the force-frequency relationship of

the patient.

10 The system records the points of the force-frequency relationship by successive

beats from which it then derives a diagram of the force-frequency relationship

over predetermined time periods.

The apparatus then compares the points of the force-frequency relationship with

the memorized regions of the force-frequency relationship in which the normal

15 and abnormal regions are defined.

If the point on the force-frequency relationship is within an abnormal region of

the force-frequency relationship, specific provisions are adopted or an appropriate

therapeutic regime is initiated. If instead the point on the force-frequency

relationship is within a normal region of the force-frequency relationship, no

20 specific provision is necessary.

However, if the point on the force-frequency relationship is within a normal

region of the force-frequency relationship but the patient is in any event

experiencing a decompensation situation, an appropriate therapeutic regime can

be initiated.

6

The definition of abnormality or normality of the force-frequency relationship

changes depending on the particular physiopathological conditions of an

individual.

If a worsening of chronic heart failure occurs, a memory permanently memorizes

5   it as an item of timed data plus a series of timed data leading up to the worsening.

Overall this series of timed data provides a definition of passage from the

generally normal component of the force-frequency relationship to the generally

abnormal component of the force-frequency relationship.

This passage enables a future worsening of chronic heart failure to be predicted

10   and to identify a current phase of worsening of chronic heart failure.

This comparison shows if the person is again experiencing an impelling condition

of worsening of chronic heart failure.

As a further advantage, the abnormality region of the force-frequency relationship

can be divided into a plurality of abnormal sub-regions. Each of these sub-regions

15   corresponds to a therapeutic regime. In addition, the therapeutic regimes can have

a structure which involves progressive increments of aggressiveness.

Additionally, the selective activation of the therapeutic regimes minimizes non-

essential energy consumption and diagnostic activity, and hence conserves the life

of the energy source.

20   Monitoring the patient's conditions not only enables his condition to be verified in

terms of identifying an abnormal situation not in itself critical but predictive of a

future worsening of chronic heart failure, but in particular enables the

effectiveness of therapies to be verified and their influence on the patient's

condition under conditions of normality.

In this respect, a sufferer from chronic heart failure can be in a negative slope

phase of his force-frequency relationship only for a fraction of the 24 hours in a

day, depending on his specific activity during certain periods of the 24 hours.

In other words, the sufferer can present a compensated behaviour in certain

5   situations, for example when seated or walking slowly, but decompensation if

climbing stairs, running or performing certain activities.

As distribution of the daily activities of the patient is variable, during the day the

patient experiences, depending on the activities normally performed, periods in

which his force-frequency relationship is of positive slope and periods in which

10   his force-frequency relationship is of negative slope or flat.

Without altering his habitual way of life, the object of the therapy is to increase

periods of compensation relative to periods of decompensation.

If for example the patient presents negative slope phases of his force-frequency

relationship lasting a total of six hours in twenty-four, an effective therapy would

15   decrease the total duration of the negative slope phases, whereas an unsuitable

therapy would increase the total duration of the negative slope phases.

Known check up systems do not enable therapy effectiveness to be verified other

than by occasional checks on the patient under rest conditions.

Therapy effectiveness is verified by checking only the resting points of the force-

20   frequency curve .

Any therapy correction made on the basis of these checks is therefore often

untimely.

8

By monitoring in accordance with the invention, not only can positive or negative decompensation changes as a result of certain events be determined, but also the variation in the force-frequency curve over twenty-four hours.

A three-dimensional diagram is hence determined which for each heart rate not only indicates the instantaneous force value but also enables the variation of said value with time to be monitored.

If the curve of force variation at a determined heart rate during the course of the day is reproduced as a two-dimensional diagram, it gives a continuous indication of the progress of decompensation situations in response to the therapies adopted.

According to the invention, the force information is derived from intracardiac pressure curves, or from peripheral pressure curves, or from ventricular volumes, or from the pressure/volume relationships, or from cardiac tone, or via impedance, or by Doppler flow measurement, or by echo-Doppler, or by a combination of all the described parameters, or by each combination of the described parameters.

The invention comprises a data processing circuit incorporated into the apparatus to receive internal or subcutaneous or external ECG electrical signals.

The circuit output can be fed to an analog/digital converter under the control of a microprocessor to convert the signals to digital data.

Associated with the microprocessor there is a memory for memorizing the digital data in ordered manner, which memorized data can be also read remotely by a telemetric connection.

The apparatus, comprising a microprocessor, can be programmed to initiate data memorization when a decompensation phase arises.

The microprocessor which controls the apparatus operation also comprises a

memory containing an instruction program to be executed by the microprocessor.

The memory is suitable for storing digital information reaching it from an

analog/digital conversion module.

5   The invention also comprises the apparatus for implementing the method, the

essential characteristics of which are defined in the claims.

According to the invention, at least one sensor emitting ventricular force-

indicative signals deriving from direct or indirect measurements thereof is

associated with an ECG sensor arranged to measure cardiac electrical activity and

10   to emit electrical signals indicative thereof.

Said signals emitted by said sensors are transformed from analog to digital by

known means, and fed to a processor which processes them to obtain a force-

frequency curve, and the variations thereof with time.

The sensors which emit signals indicative of the ventricular force are chosen from

15   one or more of the following, possibly in combination.

Said sensors can comprise an intracardiac or external pressure sensor, or an

external or internal ventricular volume sensor of the type known to the expert of

the art, or the combination of a pressure sensor and a volume sensor.

There can also be provided an internal or external sensor for sensing cardiac force

20   of contraction and/or the rate of tension development (cardiac tone and/or calcium

transient), or an impedance measurement sensor of known type.

A Doppler sensor can also be used consisting of one or more piezoelectric crystals

which determine:

- cardiac output

- stroke volume

- diastolic mitral flow measurement and systolic mitral regurgitation flow measurement

- mitral regurgitation curve and dP/dt derivative

5   - E wave deceleration time

- mitral A wave duration and duration of pulmonary venous regurgitation AR wave during atrial contraction, to establish relative A wave and AR wave duration.

It is sometimes convenient to use an implanted or external echo sensor consisting

10   of one or more piezoelectric crystals which determine the dimensions of the cardiac chambers during the cardiac cycle.

The echo sensor and the Doppler sensor are sometimes used in combination, they consisting of one or more piezoelectric crystals for the combined determination of the intracardiac flow signals and the dimensions of the cardiac chambers.

15   The following examples, illustrated by the accompanying drawings, provide a better understanding of the invention.

EXAMPLE 1 (illustrated in Figure 1) Normal subject.

X-axis: heart rate bpm, (beats per minute)

Y-axis: ventricular force expressed as dP/dt/ EDV = maximal rate of left

20   ventricular pressure development divided by end-diastolic volume (EDV) or expressed as sP/ESV = left ventricular end-systolic pressure volume ratio (end-systolic ventricular pressure divided by the end-systolic volume).

Values of ventricular force in each plot are normalized with respect to the corresponding value at 60 bpm.

During progressive physical activity, in the physiological rate range between 60

and 180 bpm, the force-frequency relationship is constantly ascending.

The slope of the sP/ESV curve is less than the slope of the dP/dt/EDV curve.

EXAMPLE 2 (illustrated in Figure 2) Diabetic cardiomyopathy.

5   X-axis: heart rate bpm, (beats per minute)

Y-axis: ventricular force expressed as dP/dt/ EDV = maximal rate of left

ventricular pressure development divided by end-diastolic volume (EDV)

or expressed as sP/ESV = left ventricular end-systolic pressure volume ratio (end-

systolic ventricular pressure divided by the end-systolic volume).

10   Values of ventricular force in each plot are normalized with respect to the

corresponding value at 60 bpm.

The force-frequency relationship within the rate range between 60 and 170 bpm is

described by a curve which ascends between 60 and 110 bpm, is flat between 110

and 130 bpm, and descends between 130 and 170 bpm.

15   For frequencies higher than 130 bpm the cardiac intropism (dP/dt) decreases with

increasing end-diastolic valume of the left ventricle (EDV); simultaneously the

systolic pressure (sP) decreases and the left ventricle lowerly empties during

systole (with increase in ESV).

EXAMPLE 3 (illustrated in the accompanying Figure 3) Mitral regurgitation.

20   X-axis: heart rate bpm, (beats per minute)

Y-axis: ventricular force expressed as dP/dt/ EDV = maximal rate of left

ventricular pressure development divided by end-diastolic volume (EDV)

or expressed as sP/ESV = left ventricular end-systolic pressure volume ratio (end-

systolic ventricular pressure divided by the end-systolic volume).

12

Values of ventricular force in each plot are normalized with respect to the

corresponding value at 60 bpm.

The force-frequency relationship within the rate range between 60 and 160 bpm is

described by a curve which ascends between 60 and 110 bpm, is flat between 100

5   and 120 bpm, and descends between 120 and 160 bpm. The force of the force-

frequency relationship increases modestly between 60 and 100 bpm. For

frequencies higher than 120 bpm the decrease in ventricular force is consistent

and for frequencies higher than 130 bpm the value is less than basal. This event

corresponds clinically to exertional dyspnea typical of this pathology.

10   EXAMPLE 4 (illustrated in the accompanying Figure 4) Dilated cardiomyopathy.

X-axis: heart rate bpm, (beats per minute)

Y-axis: ventricular force expressed as dP/dt/ EDV = maximal rate of left

ventricular pressure development divided by end-diastolic volume (EDV)

or expressed as sP/ESV = left ventricular end-systolic pressure volume ratio (end-

15   systolic ventricular pressure divided by the end-systolic volume).

Values of ventricular force in each plot are normalized with respect to the

corresponding value at 60 bpm.

The peak of the force-frequency relationship is sufficiently displaced towards low

frequencies to have a negative slope over the almost entire range of frequencies in

20   vivo (between 80 and 150 bpm). The reduction in contractile force as soon as the

heart rate increases predisposes the ventricle to dilation because of venous

overloading with increase in end-diastolic pressure. Because of the pejorative

effect of inversion of the force-frequency relationship, a therapy is advisable

which decreases heart rate.

13

EXAMPLE 5 (illustrated in the accompanying Figure 5) The dilated

cardiomyopathy of Example 4 during therapy with beta blockers.

X-axis: heart rate bpm, (beats per minute)

Y-axis: ventricular force expressed as dP/dt/ EDV = maximal rate of left

5   ventricular pressure development divided by end-diastolic volume (EDV)

or expressed as sP/ESV = left ventricular end-systolic pressure volume ratio (end-

systolic ventricular pressure divided by the end-systolic volume).

Values of ventricular force in each plot are normalized with respect to the

corresponding value at 45 bpm.

10   The bradycardia induced by the beta blocking therapy was sufficient to reposition

the operative range of the heart at low rate levels (between 50 and 100 bpm), and

the negative part of the force-frequency relationship is avoided.

The same therapeutic result is obtained in a subject not in spontaneous heart rate

when electrically stimulated while maintaining the pacing rate between 50 and

15   100 beats per minute.

EXAMPLE 6 (illustrated in Figure 6) Increase in heart rate produced by pacing in

resting patients.

X-axis: pacing frequency bpm, (beats per minute)

Y-axis: ventricular force expressed as dP/dt/ EDV = maximal rate of left

20   ventricular pressure development divided by end-diastolic volume (EDV).

Values of ventricular force in each plot are normalized with respect to the

corresponding value at 80 bpm.

Increase in heart rate produced by pacing in non-exercising subjects to assess the

force-frequency relationship at rest. Pacing was initiated at 80 bpm and increased

in definite increments up to peak pacing rate (peak pacing rate = the heart rate at

which either second-degree atrioventricular block or pulsus alternans occurred).

Cardiac output remains constant despite the pacing induced tachycardia, and the

end-diastolic volume diminishes as pacing frequency increases.

5   Patient 1: the heart is normal (Normal) and the slope of the force-frequency

relationship is positive.

Patient 2: a case with severe left ventricular hypertrophy (LVH). The force-

frequency relationship is biphasic, with an initial positive slope (ascending limb),

and subsequent negative slope (descending limb). Critical heart rate is between

10   100 and 130 bpm.

Patient 3: a case with dilated cardiomyopathy (DCM) exibited a flat force-

frequency relationship with a descending limb at higher frequencies.

CLAIMS

1   A method for the diagnosis and therapy of chronic heart failure comprising

continuous monitoring of the patient and continuous determination of significant

decompensation parameters during a sample period of normal patient life,

5   recording the data determined, continuously monitoring these data during therapy,

comparing the memorized data with those determined during the same time span

of the sample period and comparing the duration of periods in which

decompensation is present with the total duration of those periods during which

decompensation is absent or conforms to that determined during the sample

10   period.

2   A method as claimed in claim 1 characterized in that the continuous

monitoring of the patient and continuous determination of significant

decompensation parameters are made when the patient's heart rate is produced by

electrical pacing.

15   3.   A method as claimed in claim 1, characterised in that while monitoring

during therapy, all abnormal events are recorded, as well as the parameters

determined in the immediately preceding period.

4.   A method as claimed in claim 3, characterised in that should the parameters

determined in the immediately preceding period reappear, an abnormality

20   situation is indicated.

5. A method as claimed in claim 1, characterised in that the memorized

parameters are the heart rate, the ventricular contractile force, and the curve of

force variation as a function of heart rate.

6. A method as claimed in claim 5, characterised in that the memorized parameters are the heart rate, the ventricular contractile force, and the curve of force variation as a function of heart rate at determined moments of the sample period.

7. A method as claimed in claim 5, characterised by memorizing the force-frequency curve variations at least during a period equal to the sample period.

8. A method as claimed in claim 5, characterised in that the force data are derived from the intracardiac pressure curves.

9. A method as claimed in claim 5, characterised in that the force data are derived from the peripheral pressure curves.

10. A method as claimed in claim 5, characterised in that the force data are derived from the ventricular volumes.

11. A method as claimed in claim 5, characterised in that the force data are derived from the pressure/volume relationship.

12. A method as claimed in claim 5, characterised in that the force data are derived from cardiac tone (force of contraction and/or rate of tension development).

13. A method as claimed in claim 5, characterised in that the force data are derived via impedance.

14. A method as claimed in claim 5, characterised in that the force data are derived from Doppler flow measurement.

15. A method as claimed in claim 5, characterised in that the force data are derived with echo-Doppler.

17

16.   A method as claimed in claim 5, characterised in that the force data are

derived from a combination of all or part of the following parameters: the

intracardiac pressure curves, the peripheral pressure curves, the ventricular

volumes, the pressure/volume relationship, the cardiac tone, the impedance, the

Doppler flow measurement, the echo-Doppler measurement.

17.   A method as claimed in claim 5, characterised in that the ventricular force is

expressed as dP/dt/EDV, which indicates the maximal rate of left ventricular

pressure development divided by end-diastolic volume (EDV).

18.   A method as claimed in claim 5, characterised in that the ventricular force is

expressed as sP/ESV, which indicates the left ventricular end-systolic pressure

volume ratio (end-systolic ventricular pressure divided by the end-systolic

volume).

19.   A diagnostic apparatus characterised by comprising at least one sensor

which emits a signal proportional to the ventricular force and an ECG sensor

arranged to measure cardiac electrical activity, both emitting electrical signals

indicative of cardiac activity; an analog/digital converter to convert the sensor

signals into digital data; an electronic processor programmed to process the

determined data and to trace a force-frequency curve; a memory for storing the

digital data in an ordered manner; and a comparator for comparing ordered

successions of digital data stored in the memory with ordered successions of

instantaneously determined digital data.

20.   An apparatus as claimed in claim 19, characterised in that the sensor which

emits signals proportional to pressure is intracardiac.

18

21.   An apparatus as claimed in claim 19, characterised in that the sensor which

emits signals proportional to pressure is external.

22.   An apparatus as claimed in claim 19, characterised by comprising a

ventricular volume sensor.

23.   An apparatus as claimed in claim 19, characterised in that the sensor which

emits signals proportional to the pressure/volume relationship is a combination of

a pressure sensor and a volume sensor.

24.   An apparatus as claimed in claim 19, characterised by comprising an

internal or external sensor for determining the force of contraction and/or the rate

of tension development (cardial tone and/or calcium transient).

25.   An apparatus as claimed in claim 19, characterised by comprising a sensor

for determining impedance.

26.   An apparatus as claimed in claim 19, characterised by comprising a Doppler

sensor consisting of one or more piezoelectric crystals which determine one or

more of the following parameters:

- cardiac output

- stoke volume

- diastolic mitral flow measurement and systolic mitral regurgitation flow

measurement

- mitral regurgitation curve and dP/dt derivative

- E wave deceleration time

- mitral A wave duration and duration of pulmonary venous regurgitation AR

wave during atrial contraction, to establish relative A wave and AR wave

duration.

19

27.   An apparatus as claimed in claim 19, characterised by comprising an

implanted or external sensor consisting of one or more piezoelectric crystals

which determine the dimensions of the cardiac chambers during the cardiac cycle.

28.   An apparatus as claimed in claim 19, characterised by comprising an echo-

5   Doppler sensor consisting of one or more piezoelectric crystals for the combined

determination of the intracardiac flow signals and the dimensions of the cardiac

chambers.

29.   An apparatus as claimed in claim 19, characterised in that the ECG sensor is

internal.

10   30.   An apparatus as claimed in claim 19, characterised in that the ECG sensor is

subcutaneous.

31.   An apparatus as claimed in claim 19, characterised in that the ECG sensor is
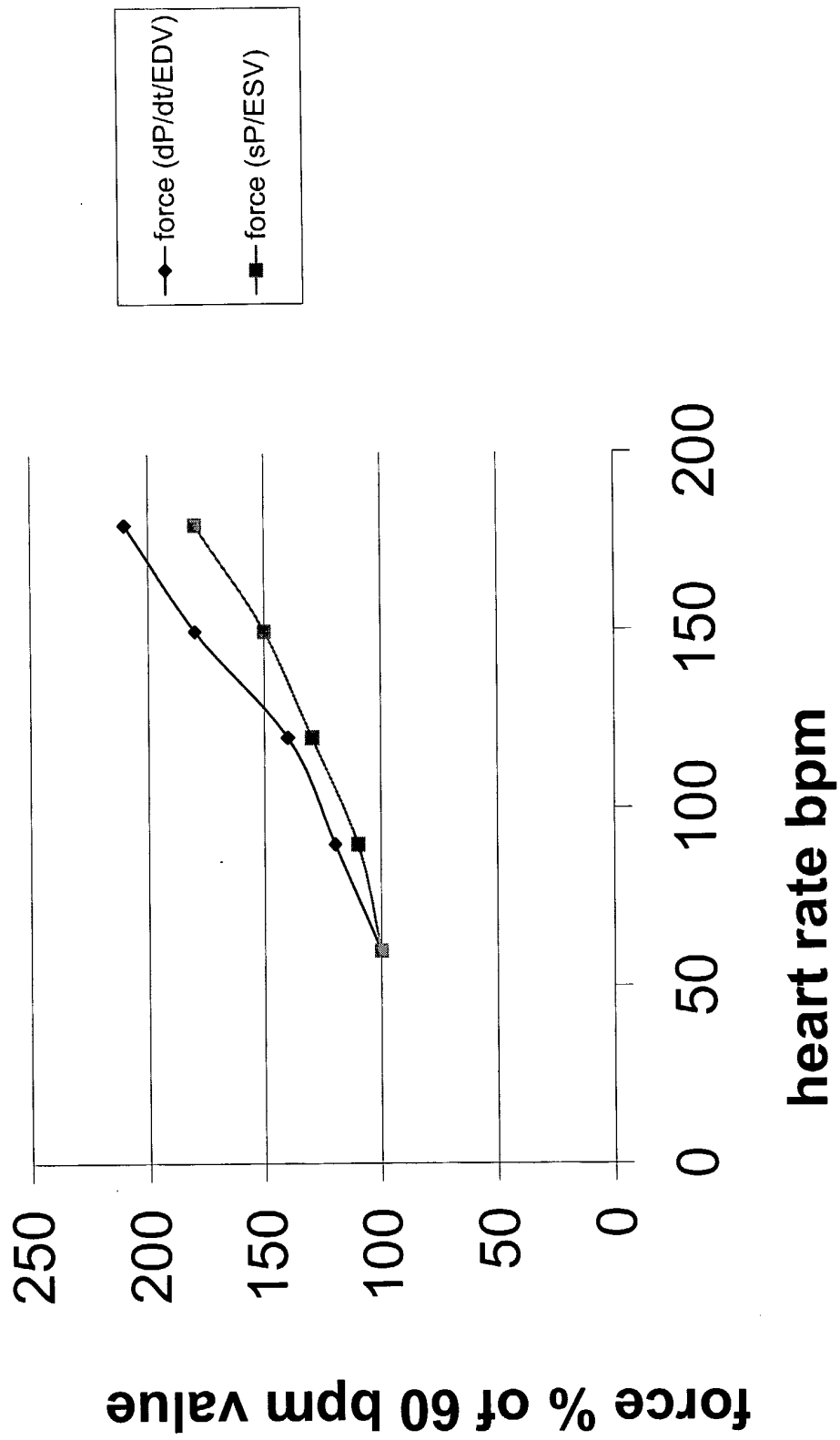
external.
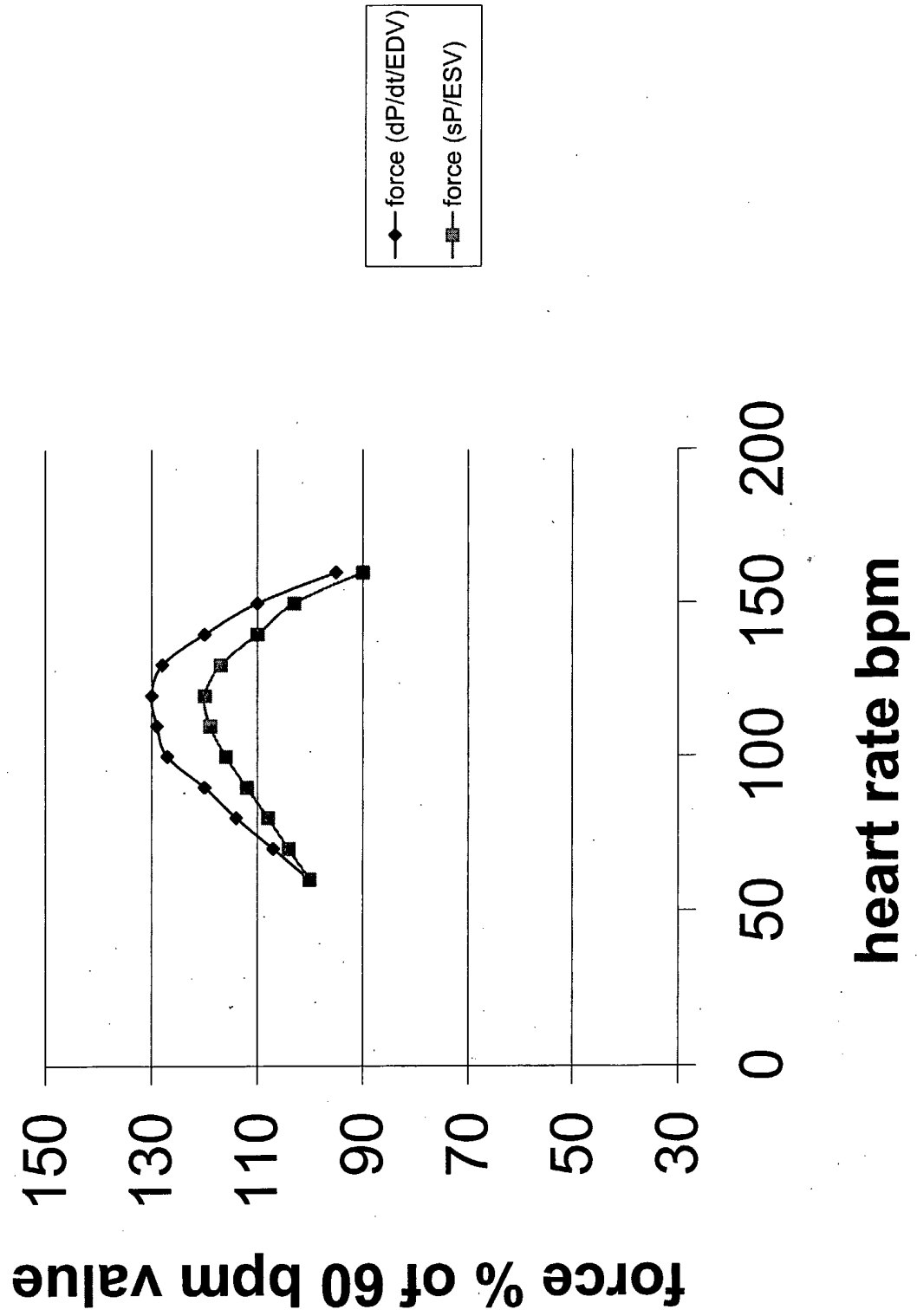
Fig. 1 Normal

Fig. 2 Diabetic cardiomyopathy
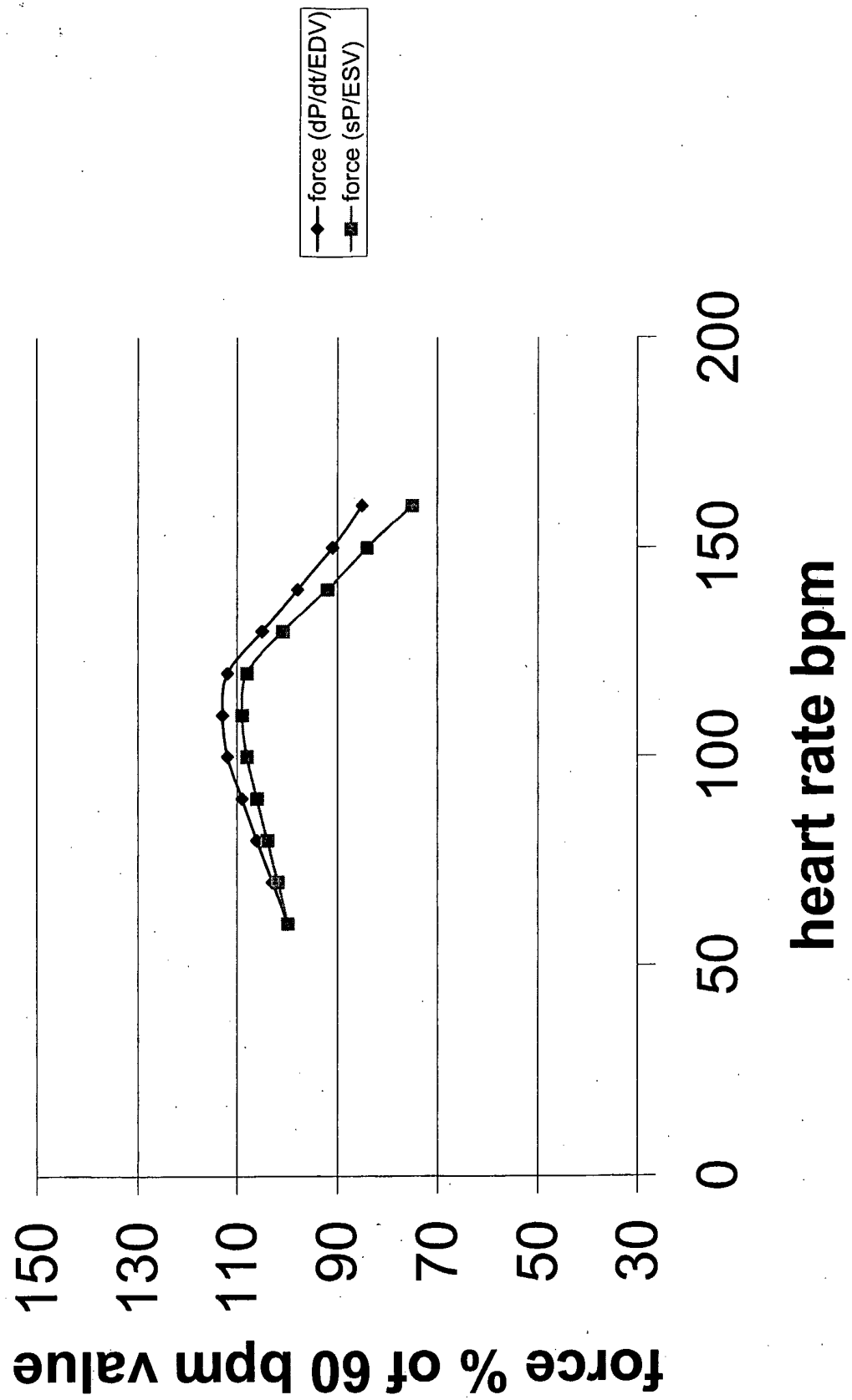
Fig. 3 Mitral regurgitation

Legend: force (dP/dt/EDV); force (sP/ESV)

X-axis: heart rate bpm (0, 50, 100, 150, 200)

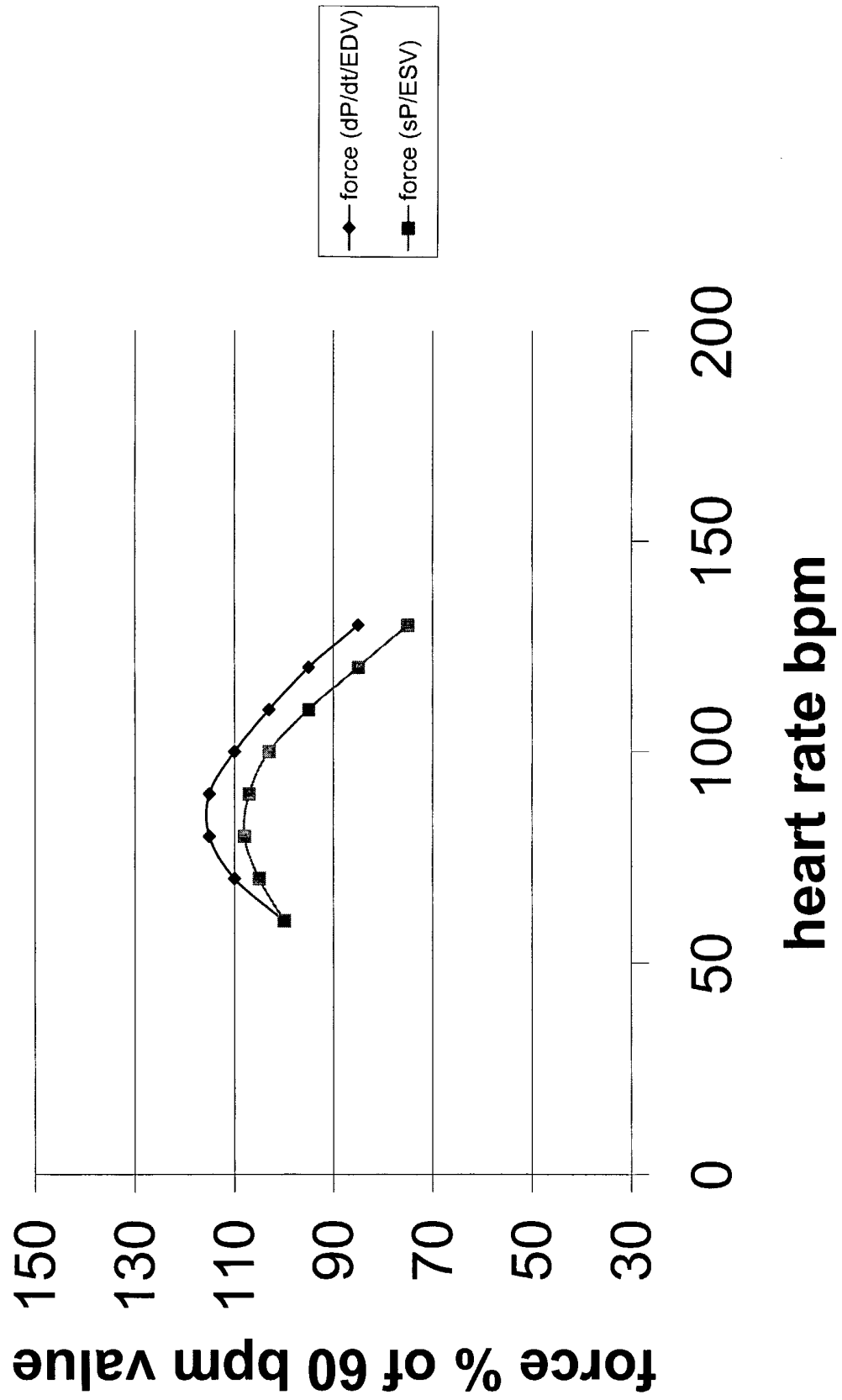Y-axis: force % of 60 bpm value (30, 50, 70, 90, 110, 130, 150)

Fig. 4 Dilated cardiomyopathy

Fig. 5 Dilated cardiomyopathy (beta blockers on)
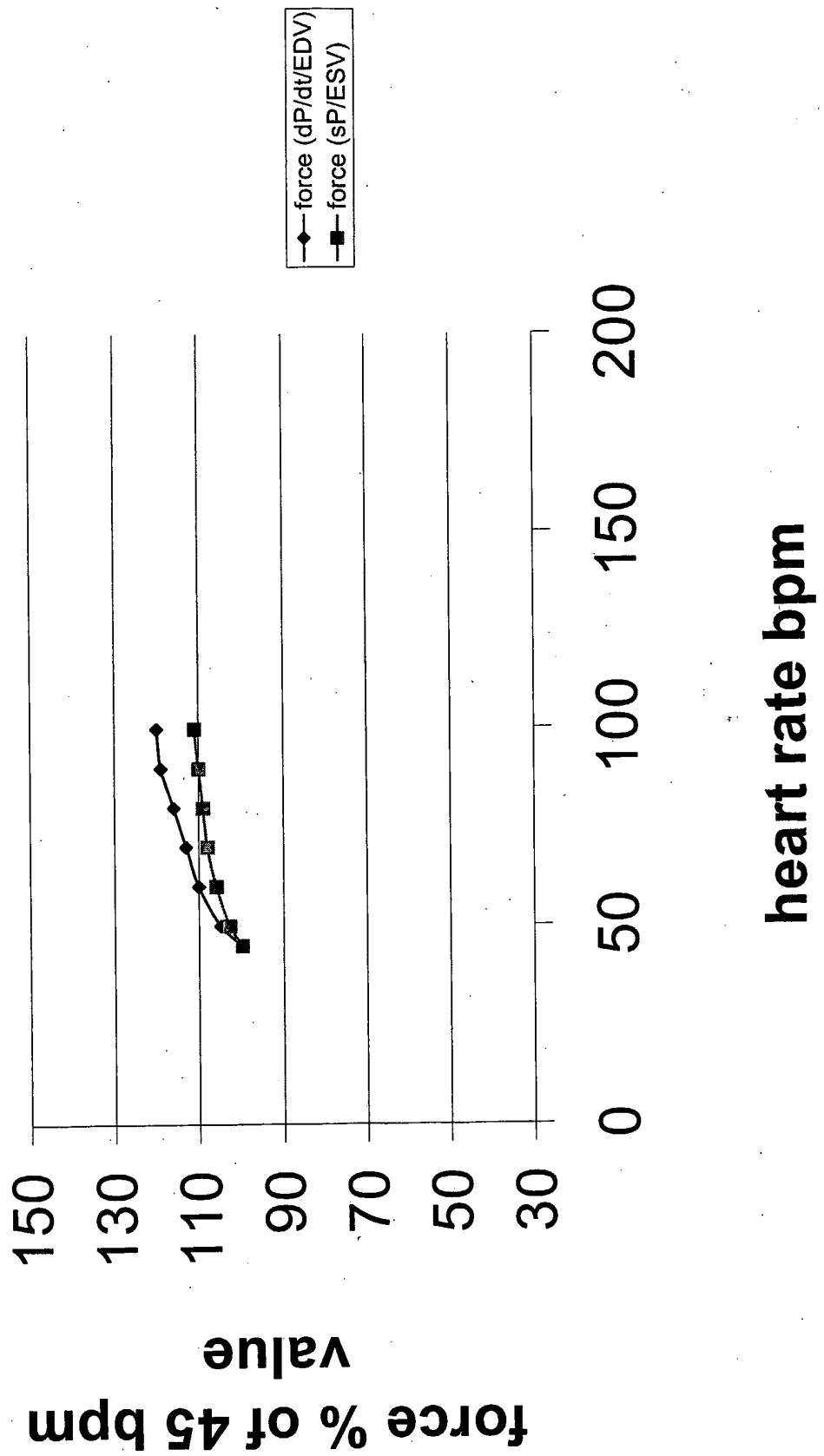
Fig. 6 - Increase in heart rate produced by pacing in resting patients

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7   A61B5/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7   A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 584 298 A (KABAL JOHN) 17 December 1996 (1996-12-17) abstract; figure 14	19
A	EP 0 651 970 A (ROBIN MEDICAL TECHN LTD) 10 May 1995 (1995-05-10) abstract; claim 1; figure 11	19
A	WO 99 12468 A (KUNIG SABINE VIVIAN) 18 March 1999 (1999-03-18) abstract	19
A	US 5 370 122 A (KUNIG HORST E ET AL) 6 December 1994 (1994-12-06) figure 2	19
A	US 5 178 154 A (ACKMANN JAMES J ET AL) 12 January 1993 (1993-01-12)	

-/--

[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 2002	11/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Papone, F

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No

PCT/EP 01/14196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 014 852 A (AHER ANTS ;SILEM HEIKI (EE); LAMP JUERGEN (EE); KOEOEBI TIIT (FI)) 5 July 2000 (2000-07-05) -----	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5584298	A	17-12-1996	WO	9820791 A1	22-05-1998
			US	5743268 A	28-04-1998
			AU	7722496 A	03-06-1998
EP 0651970	A	10-05-1995	EP	0651970 A1	10-05-1995
			JP	7184868 A	25-07-1995
			US	5634467 A	03-06-1997
WO 9912468	A	18-03-1999	WO	9912468 A1	18-03-1999
US 5370122	A	06-12-1994	EP	0670694 A1	13-09-1995
			WO	9410903 A1	26-05-1994
US 5178154	A	12-01-1993	NONE		
EP 1014852	A	05-07-2000	EP	1014852 A1	05-07-2000
			US	6228033 B1	08-05-2001
			WO	9851211 A1	19-11-1998