Wolfgang Krüger

Acute Heart Failure

Putting the Puzzle of Pathophysiology and Evidence Together in Daily Practice

Second Edition

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Foreword to the Second Edition

Since the publication of the first edition in 2009, quite a substantial amount of new insights in the pathobiology of acute heart failure have been gained. This second edition incorporates these new findings and integrates them into the "big puzzle" and concept of acute heart failure syndromes. Indeed, we have not only discovered more details about this syndrome but this new knowledge substantially helps us to understand the overall context of this malady. The new views may hopefully open ways to develop new and better therapeutic strategies, particularly for patients with heart failure and preserved ejection fraction where a scientifically based effective treatment could not yet be established.

Aarau, Switzerland — Wolfgang Krüger

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Abbreviations

A II	Angiotension II
ACCP	American College of Chest Physicians
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHA	American Heart Association
AHF	Acute heart failure
AHFS	Acute heart failure syndromes
AKI	Acute kidney injury
AMI	Acute myocardial infarction
AR	Aortic valve regurgitation
ARBs	Angiotension receptor blockers
ARDS	Acute respiratory distress syndrome
ATN	Acute tubular necrosis
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CF	Cardiac function
cGMP	Cyclic guanosine monophosphate
CI	Cardiac index
CO	Cardiac output
COPD	Chronic obstructive lung disease
CPI	Cardiac power index
CPO	Cardiac power output
CPP	Coronary perfusion pressure
CRS	Cardio-renal syndrome
CS	Cardiogenic shock
CVP	Central venous pressure
DD	Diastolic dysfunction
DOB	Dobutamine
dp/dt	Change in (left) ventricular pressure per time
DPG	Diastolic pressure gradient (or difference)
DVI	Diastolic ventricular interaction

Ea	Effective arterial elastance
ECM	Extracellular matrix
ED	Endothelial dysfunction
Ees	End-systolic chamber elastance
EF	Ejection fraction; ejection fraction of the left ventricle mainly named EF, but sometimes also LV-EF; RV-EF (ejection fraction right ventricle)
ESC	European Society of Cardiology
ESV	End-systolic volume
EVLW(I)	Extra vascular lung water (index)
FS	Fractional shortening
GEDV	Global end diastolic volume
GFR	Glomerular filtration rate
HF	Heart failure
HFpEF	Heart failure with preserved EF
HFrEF	Heart failure with reduced EF
HHD	Hypertensive heart disease
HR	Heart rate
HTN	Hypertension
ICP	Intracerebral pressure
IHD	Ischemic heart disease
IL-6	Interleukin 6
IR	Insulin resistance
ITBV(I)	Intrathoracic blood volume (index)
IVS	Interventricular septum
i.v.	intravenous
LA	Left atrium
LA-P	Left atrial pressure
LAVI	Left atrial volume index
LEVO	Levosimendan
LHD	Left heart disease
LV	Left ventricle
LVEDA	Left ventricular end-diastolic area
LVEDD	Left ventricular end-diastolic diameter
LVEDP	Left ventricular end diastolic pressure; also called intracavitary LVEDP
LVESP	End-systolic left ventricular pressure
LVESV	End-systolic left ventricular volume
LV-H	Left ventricular hypertrophy
LVMI	Left ventricular muscle mass index
LVOT	Left ventricular outflow tract
LMWH	Low molecular weight heparin
MAP	Mean arterial (blood) pressure
mPAP	Mean pulmonary arterial pressure
MR	Mitral valve regurgitation

NA	Noradrenaline, also called norepinephrine (NE)
NHs	Neurohormonal systems
NO	Nitric oxide
NT-pro BNP	N-terminal pro b-type natriuretic peptide
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
mPAP	mean pulmonary artery pressure
PBV	Pulmonary blood volume
PCWP	Pulmonary capillary wedge pressure
PE	Pulmonary embolism
PEEP	Positive end-expiratory pressure
PH	Pulmonary hypertension
PKG	Proteinkinase G
PLR	Passive leg raising
PP	Pericardial pressure
PP-V	Pulse pressure variation
P-V relationship	Pressure-volume diagram of the ventricle cycle
PvH	Pulmonary venous hypertension
PvP	Pulmonary venous pressure
PVPI	Pulmonary venous permeability index
PVR	Pulmonary vascular resistance
RA	Right atrium
RAAS	Renin-angiotensin-aldosterone system
RA-P	Right atrial pressure
RBF	Renal blood flow
RCA	Right coronary artery
RHF	Right heart failure
ROS	Reactive oxygen species
RV	Right ventricle
RV-F	Right ventricular failure
RV-AMI	Acute myocardial infarction of the right ventricle
RV-D	Right ventricular dysfunction
RVEDD	Right ventricular end-diastolic diameter
RVEDP	Right ventricular end diastolic pressure
RVEDV	Right ventricular end diastolic volume
sBP	Systolic blood pressure
s.c.	subcutaneous (injection)
$ScvO_2$	Central venous oxygen saturation (central vein, i.e. vena cava inferior)
SIR	Systemic inflammatory response
SIRS	Systemic inflammatory response syndrome
SP-V	Systolic pressure variation
SV(I)	Stroke volume (index)
SvO_2	Mixed venous oxygen saturation (pulmonary artery)

SVR(I/i)	Systemic vascular resistance (index)
SV-V	Stroke volume variation
SW(I)	Stroke work (index)
TGF	Tubuloglomerular feedback
TNF_{α}	Tumor necrosis factor α
TPG	Transpulmonary pressure gradient
TPR	Total peripheral resistance (which is the same as SVR)
UO	Urinary output
v-a-coupling	Ventriculo-arterial coupling
VT	Ventricular tachycardia
WU	Wood unit (dyn s cm^{-2})

Contents

Cardiac Physiology and Acute Heart Failure Syndromes

1

1.1 Cardiac Performance

Cardiac performance depends on a wide variety of factors, of which preload, afterload, heart rate, and contractility are the best recognised (Fig. 1.1). However, other factors play important roles but are less acknowledged. The diastolic ventricular interaction (DVI) and its impact on preload, the preload recruitable stroke-work,

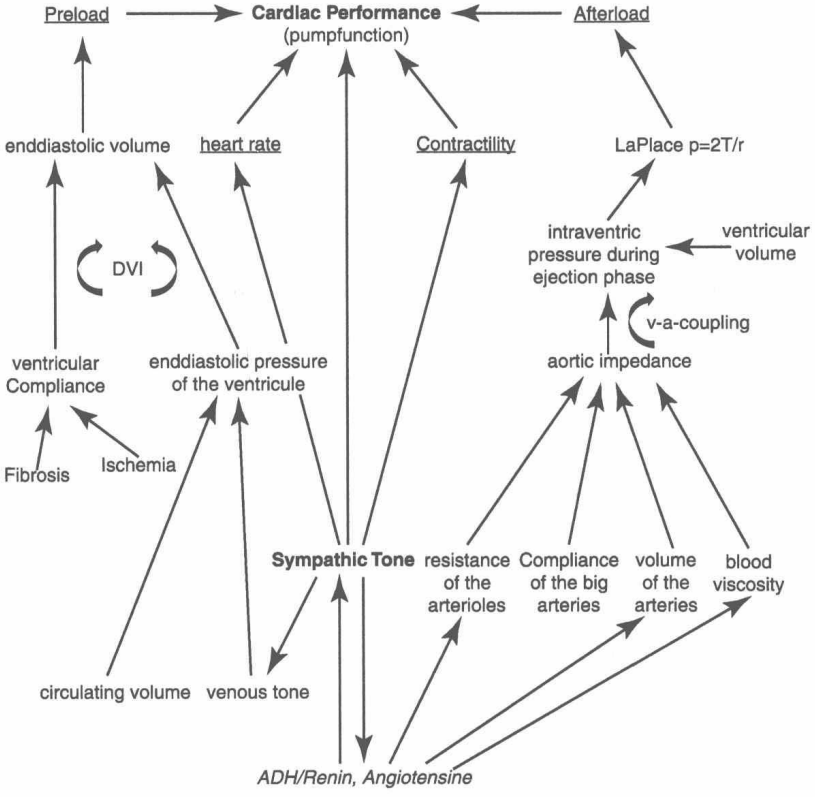

Fig. 1.1 The modified diagram by Gould and Reddy, "Vasodilator Therapy for Cardiac Disorders", Futura, Mount Kisco, New York, 1979, pp 1-6, illustrates the complex interplay of factors affecting cardiac performance. With permission

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ventriculo-arterial coupling and other vascular and ventricular properties, through their interaction at end-systole, all have significant influence on cardiac performance.

1.2 The Fundamental Equation of the Circulation

$$MAP = CO \times SVR \left(\text{Pressure} = \text{Flow} \times \text{Resistance}\right) \text{ [1, 2]}$$

The fundamental equation of the circulatory system expresses the basic function of the heart: to generate flow and pressure in order to ensure appropriate perfusion of the body [3, 4].

The systemic peripheral resistance, difficult to determine directly in practice, can be calculated by using the measurable parameters of MAP and CO. However the SVR is not determined by them, **SVR and CO are independent, the MAP is the dependent variable** [5].

Poiseuille's law offers three ways to change blood pressure [6, 7]:

- alter flow,
- alter resistance,
- alter both.

Thus, increased blood flow and/or an increased ratio of resistance/blood flow (SVR/CO) can alter the MAP [8]. If CO and SVR change reciprocally and proportionately, only then will the MAP be unchanged. If CO increases but with a reduction of SVR due to peripheral vasodilatation, MAP will increase if the increase in CO is proportionately higher than the reduction of SVR. In the case of volume loading, increasing CO will lead to an increase in MAP if SVR remains unchanged [5].

Kumar showed that volume loading in **healthy hearts** increases contractility, stroke work, systolic blood pressure, **and MAP** [9]. However, in the heart with compromised contractility, blood pressure might not increase. Michard [10] showed that the increase in SV (flow) depends critically on the contractile abilities of the heart. Thus, if volume loading does not lead to an increase in SV, we should be suspicious of significant heart failure. Furthermore, we should keep in mind that, in heart failure syndromes, the **LV afterload** is the decisive determinant of cardiac performance [11–14]. Therefore, a reduction in afterload by vasodilators is the treatment of choice [15, 16].

As a rule, in **daily clinical practice** in acute heart failure when **lowering peripheral resistance**, the LV end-systolic wall stress will be reduced and the SV will increase, but the MAP will be maintained or will even increase [17–19]. If, under these conditions, the MAP does not increase or at least cannot be maintained, the following circumstances have to be considered:

- severe mitral regurgitation [20–22],
- inappropriate filling of the LV due to DVI [23–25],

- ventriculo-arterial coupling mismatch [26, 27],
- inadequate intravascular volume (relative hypovolaemia) [28, 29]—(seldom).

1.3 Preload

1.3.1 Definition

Preload is defined by Braunwald and Ross [30] as "**the force acting to stretch the left ventricular muscle fibres at the end of diastole and determining the resting length of the sarcomeres**".

Returning venous blood fills the ventricle, exerting force on the heart muscle, stretching the myofibrils [30] and is one of the main determinants of cardiac performance [31–33].

The end-diastolic ventricular volume, or preload, is well reflected by the end-diastolic wall stress (**preload ~ end-diastolic wall stress**) [34].

1.3.2 The Frank–Starling Mechanism

Transmural LVEDP accurately reflects the effective distending pressure responsible for the length of myocardial fibres [35].

Otto Frank [36] and Ernest Starling [37] obtained a relationship between the end-diastolic fibre length and the force of contraction:

With increasing fibre length the force of contraction increases and thus the **LV or RV stroke volume (SV)** [36, 37] **increases** or, more accurately, the stroke work (SW) increases:

$$\text{LV-SW} = \text{SV} \times (\text{LVESP} - \text{LVEDP}) \text{ [38, 39]}$$

The diastolic ventricular filling is limited by the acutely non-distensible pericardium constraining the filling ventricles and by the cytoskeleton [40–42], thus preventing the ventricles from fluid overload [43, 44] (physiological protective mechanism) as well as from pathological dilatation [41].

With an increase in resting fibre length the velocity of fibre muscle shortening increases as well [45].

Frank [36] established a linear relationship between the left ventricular **end-diastolic volume** (LVEDV) as a correlate of the fibre length and the **force of ventricular contraction** [30, 36, 37, 43].

LV-SV correlates well with LVEDV: **SV ~ LVEDV** [46]

Starling [37] reported an increase in the **contraction force** with increasing atrial **pressures**. Starling's result is similar to that described by Frank, as long as the increase in LVEDP rep-resents a **roportional** increase in LVEDV (linear relationship between LVEDP and LVEDV).This is true in most healthy persons as long as the LVEDP remains within normal ranges, but in the case of high LV

filling pressures and in certain pathological circumstances the rise in LVEDP is often disproportionately high in comparison to the increase in LVEDV [23, 24, 47–49].

The LVEDP may even rise without any increase in LV filling volume, producing no increase in preload, which is essential to recruit a higher SV [23, 39, 42]. Therefore, although the LVEDP rises, there may be no adequate increase in SV; in fact, there may even be a fall corresponding with the 'descending limb' of the Starling curve [35, 37, 39, 50]. This descending limb described by Starling is, however, an artefact of his experimental conditions.

When using the **effective distending pressure** rather than the intra-cavitary pressure the relation between fibre stretch and force of contraction is described adequately and corresponds to Frank's findings and the statement:

The effective distending pressure or **'transmural' LVEDP** is the intracavitary **LVEDP** (commonly just called LVEDP) **minus** the **surrounding** pressure(s) [35].

Katz, in 1965, already assumed that intracavitary and transmural end-diastolic left ventricular pressures were only equal when the pressure surrounding the left ventricular heart muscle was negligible [35]. Otherwise the external pressure must be subtracted from the intracavitary LVEDP to calculate the effective distending or transmural pressure.

Transmural LVEDP = LVEDP – surrounding pressure [35]

Usually, the surrounding pressure has contributions of one-third by the RVEDP and two-thirds by the pericardial pressure [51, 52]:

Transmural LVEDP = intracavitary LVEDP – (2/3 pericardial pressure + 1/3 RVEDP) Under normal conditions, RAP and pericardial pressure (PP) are nearly equal [53–55] and further changes in pericardial pressure are very closely reflected by RA pressure changes [53, 56, 57].

The close relation between changes in RA pressure and pericardial pressures allows us to give a reasonable estimate of transmural pressure by subtracting RAP from pulmonary capillary wedge pressure (PCWP) [23, 53, 56]:

Transmural LVEDP = PCWP – RAP ≈ PCWP – CVP

with CVP reflecting the 'surrounding pressure' [23, 53, 56, 58, 59].

There is substantial evidence that PCWP reflects LVEDP [60–62]. CVP is measured where the vena cava leads into the right atrium [58] and, as such, equals the RAP [58, 59]. Due to the very close relations between RAP and PP ($r = 0.95$, $p < 0.005$) [63] and RAP and changes in PP [53, 56, 57] respectively, CVP is a good estimate of PP [53–55, 58, 59, 63] in daily practice. Furthermore, both, CVP and RAP reflect the RVEDP [44, 59, 63]. Over a wide range, pericardial pressure, RAP and RVEDP are literally equal [64]. Tyberg [53] demonstrated that RVEDP well represents PP in ranges between 4 and 20 mmHg. However, in case of right