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Analog Simulation of Aortic Stenosis

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1. Introduction

In cardiovascular physiology mathematical and analog simulations are well known (Beneken, 1965; Defares et al.; 1963, Grodins; 1959; Kordaš et al., 1968; Milhorn, 1966; Osborn,1967;). However, in analog modelling physical electrical models have been replaced by computer analysis of electronic analog circuitry. Then they have been applied to various physiological systems (Bošnjak & Kordaš, 2002; Dolenšek et al., 2005), to study also cardiovascular physiology (Rupnik et al., 2002), including mechanisms of compensation (Podnar et al., 2002) and principles of homeostasis, i. e. negative feedback mechanisms (Podnar et al., 2004). Recently, the equivalent circuit simulating the cardiovascular system was further upgraded to simulate, as close as possible, conditions in man in vivo. First, the intrathoracic pressure was made slightly negative and undulating at the rate of respiration. Second, the homeostasis included not only a control of venous tone and contractility of left and right ventricle, but also the control of heart rate. Third, the mean arterial pressure was - in some conditions - reset from the normal to a higher operating level (simulating increased sympathetic tone). By using these approaches recently various clinical conditions were simulated: acute left ventricle failure (myocardial infarction), aortic stenosis and exercise in man with aortic stenosis (Sever et al., 2007), and consequences of aortic and of mitral regurgitation (Dolenšek et al., 2009).

In present simulations it is attempted to extend both recent simulations quoted above. The consequences, induced by exercise in patients with aortic stenosis are to be studied in more detail. To meet this end, in aortic stenosis i) the aortic and mitral flows are studied and ii) mechanism of exhaustion, induced by exercise, are simulated.

2. Methods

Analysis of the equivalent circuit is performed by using Electronics Workbench Personal version 5.12 (Adams, 2001).

As in previous simulations four targets are modulated by negative feedback: venous tone, contractility of right ventricle, contractility of left ventricle, and heart rate. Essentially, the present equivalent circuit is the same as reported (Sever et al., 2007). The resetting of mean arterial pressure includes procedures whereby its resting value, "clamped" at about 98 mm Hg is shifted and then "clamped" again at a higher level. Heart rate control is the same as described in Sever and coworkers (Sever et al., 2007); the duration of the systole is constant,

200 ms in all simulation conditions. Mitral and aortic valve are simulated by diode D1. Input to the left ventricle is slightly modified as published (Dolenšek et al., 2009). Contractility modulation is the same as described in Sever and coworkers (Sever et al., 2007); via negative feedback it can be increased from 1 to about 8 "units of contractility". The time constant for myocardial contractility modulation control is increased from 1 s to 5 s.

Aortic stenosis is simulated as described (Sever et al., 2007). Exercise is simulated by decreasing arteriolar and capillary resistance by 50 % and by resetting mean arterial pressure. Then, via negative feedback, heart rate, myocardial contractility and venous capacitance are adjusted accordingly. Exhaustion of LV sympathetic drive is simulated by decreasing myocardial contractility modulation factor from about 8 to 1. Mild LV failure is simulated by decreasing the nominal contractility by about 50 %.

Results are expressed graphically as described (Sever et al., 2007; Dolenšek et al., 2009), as the time course of equivalent variables. Thus electrical variables voltage, current, resistance, capacitance and charge correspond to physiological variables pressure, blood flow, resistance, capacitance and volume (for details refer to Sever et al., 2007; Dolenšek et al., 2009). The acronyms used are listed below:

AoP	aortic pressure
CO	cardiac output
CVV	"contractible" volume of veins
EDVLV	end-diastolic volume of left ventricle
EFLV	left ventricle ejection fraction
ESVLV	end-systolic volume of left ventricle
ESVRV	end-systolic volume of right ventricle
ICT	isovolumetric contraction time
IRT	isovolumetric relaxation time
ITP	intrathoracic pressure
LV, LVV	left ventricle, volume of left ventricle
LAtP	left atrial pressure
LVP	left ventricular pressure
MAoP	mean arterial pressure
SVLV	stroke volume of the left ventricle
Sy	LV contractility modulation; inothropic (homeostatic) sympathetic effect on LV

Note that negative and undulating ITP affects slightly almost all variables. To allow comparison before and after a disturbance occurs, the time course of variables are recorded at the same instant of the heart cycle, defined here as the height of inspiration.

3. Results

All results are presented graphically showing the time course of variables which are of interest to be studied.

The transition of normal conditions into conditions affected by exercise are shown in Fig. 1A. The transition of normal conditions into conditions of aortic stenosis, exercise and exhaustion are shown in Fig. 2A.

The time course of these variables is also shown for systole and part of diastole. Effects of exercise are shown in Figs. 1B, C. Effects of exercise in aortic stenosis and after exhaustion are shown in Figs. 2B, C, D, E.
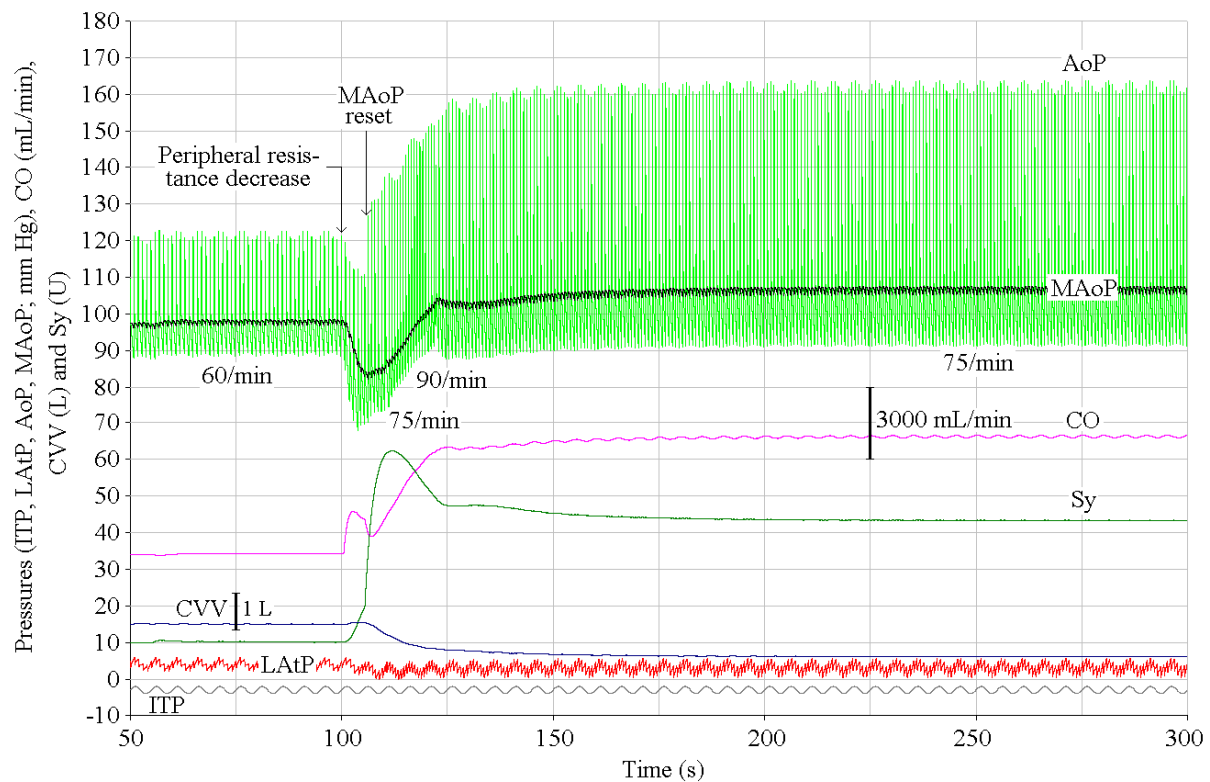
Fig. 1A. The time course of AoP, MAoP, heart rate, CO, Sy, CVV, LAtP and ITP in normal (resting) conditions and after peripheral resistance decrease (exercise; by 50 %, at 100.5 s. MAoP is reset at 105.5 s). Transiently the heart rate is increased from 60/min to 75/min and 90/min, until in steady state conditions it stabilises at 75/min. Note that despite venoconstriction (decreased CVV) LAtP is decreased. This is because Sy is increased, resulting in a strong LV contraction increase. Consequently, systolic AoP and pulse pressure is increased. There is little change in diastolic AoP. Because peripheral resistance is decreased MAoP is about 108 mm Hg and CO almost doubled.

Changes in cardiovascular variables (AoP, MAoP, CO, CVV, LAtP and ITP) in normal (resting) conditions, after peripheral resistance decrease (exercise) and after resetting of MAoP are presented in Fig. 1A. Initially (50 s - 100 s), all variables are in steady state. After peripheral resistance decrease (100 s - 300 s) the initial brief AoP and MAoP decrease are offset by MAoP reset (increased sympathetic tone). Due to venoconstriction (CVV decrease) and huge increase in Sy the force and rate of LV contraction are increased. Heart rate is increased. Consequently, CO and the systolic LVP and AoP are strongly increased.
Fig. 1B displays the time course of AoP, MAoP, LVP, LAtP, ICT, IRT, aortic and mitral flow, and various LV variables during systole and part of diastole in resting conditions (58.7 s - 59.3 s). Note that the relatively large aortic flow in early systole.
The time course of the same variables, as in Fig. 1B, during systole and part of diastole after peripheral resistance decrease (exercise; 193.3 s - 193.9 s) is shown in Fig. 1C. Comparing Figs. 1B and 1C the following changes show up: due to vigorous LV contraction ICT is drastically shortened. Aortic flow is huge and occurs early in systole. Therefore SVLV is increased, but EDVLV decreased. Consequently the early diastolic LVP is negative!
The values of AoP, MAoP, CO, CVV, LAtP and ITP in normal (resting) conditions, after induction of aortic stenosis, after peripheral resistance decrease (exercise) and resetting
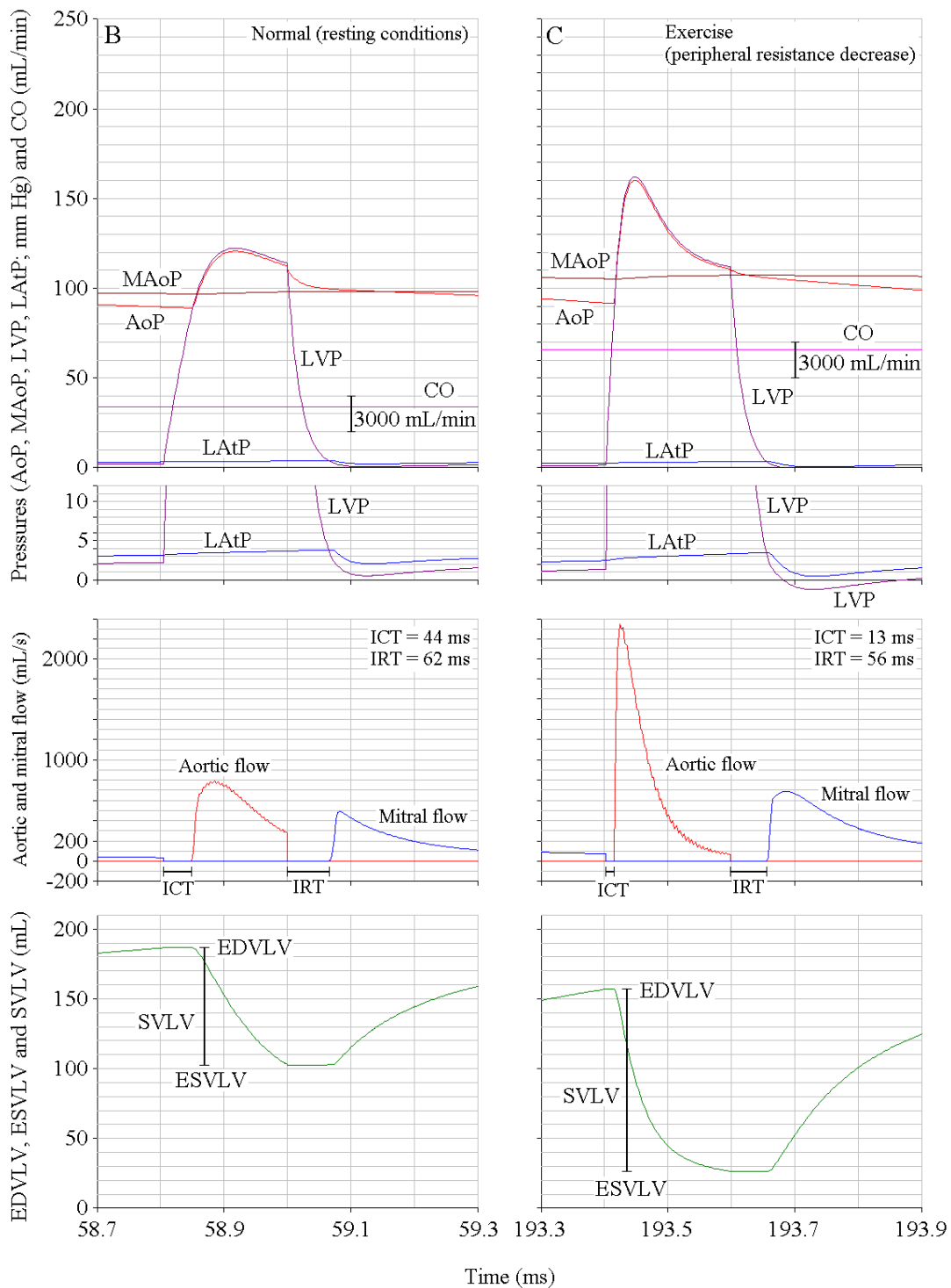
Fig. 1B, C. AoP, MAoP, LVP, LAtP, CO, (upper two blocks), aortic and mitral flow (middle block), and left ventricular volumes (bottom block) recorded during systole and part of diastole. B: Normal (resting) conditions (58.7 s - 59.3 s). Note the peak aortic flow in mid-systole and peak mitral flow in early diastole. C: Exercise (peripheral resistance decrease and MAoP reset; 193.3 s - 193.9 s). Due to a vigorous LV contraction ICT is decreased, EDVLV and ESVLV decreased and SVLV increased. Peak aortic flow occurs early in systole. Consequently, early diastolic LVP is slightly negative.

MAoP and, finally, after exhaustion of LV sympathetic drive and mild LV failure are shown in Fig. 2A. Initially (50 s - 70.5 s), all variables are in steady state. After aortic stenosis (at 70.5 s) the recorded variables are affected only transiently. After peripheral resistance decrease (100 s - 300 s) the initial brief AoP and MAoP decrease are offset by MAoP reset (increased sympathetic tone). Due to venoconstriction (CVV decrease) and huge increase in Sy the force and rate of LV contraction are increased. Heart rate is increased. Consequently, CO and the systolic LVP and AoP are strongly increased. At 200.5 s and 205.5 s, respectively, as Sy is decreased due to exhaustion and mild LV failure occurs, AoP, MAoP and CO decrease and LAtP is strongly increased.
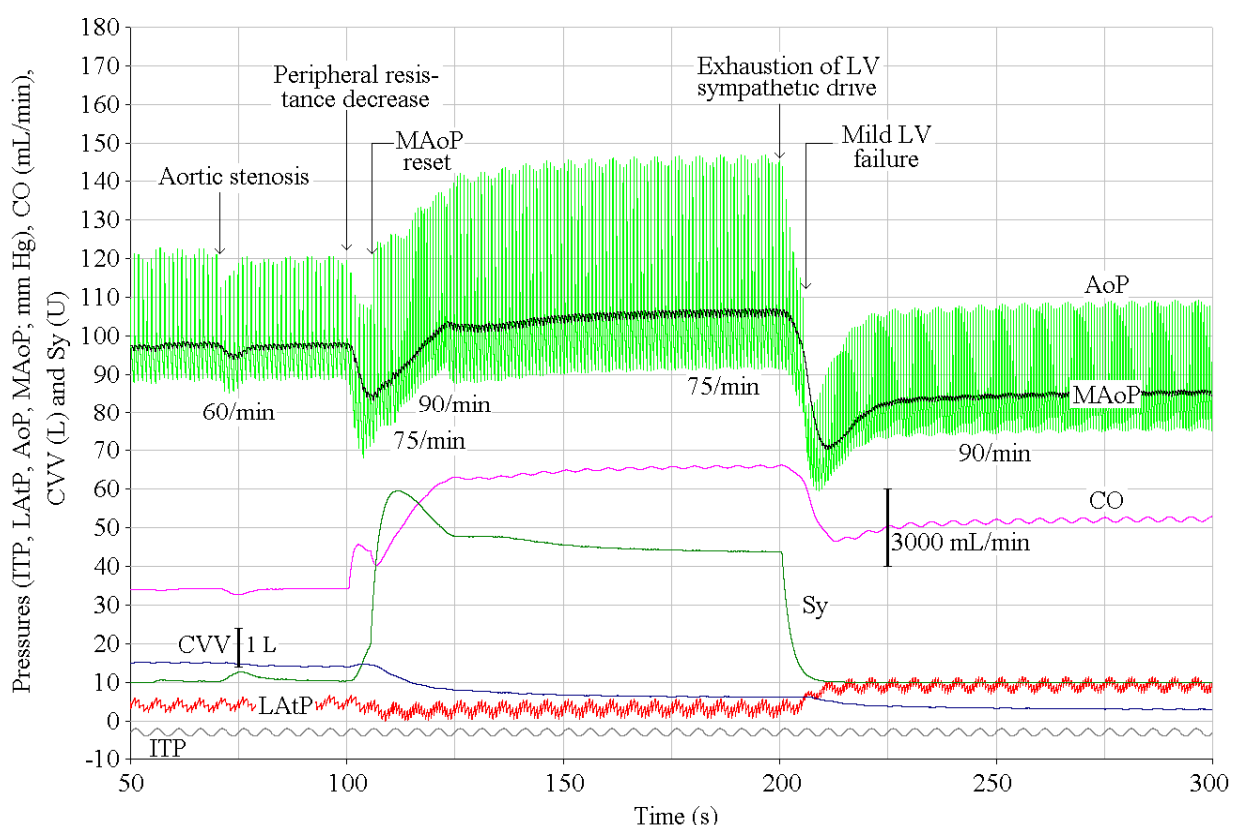

Fig. 2A. The time course of AoP, MAoP, heart rate, CO, Sy, CVV, LAtP and ITP in normal (resting) conditions, after aortic stenosis (0.08 U, at 70.5 s), after peripheral resistance decrease (exercise) and MAoP reset (by 50 % at 100.5 s and 105.5 s, respectively). Exhaustion of LV sympathetic drive and mild LV failure occur at 200.5 s and 205.5 s, respectively. Note that aortic stenosis has a small and transient effect, mainly in AoP only. The abrupt decrease in peripheral resistance results in a transient AoP and MAoP decrease and increase in heart rate from 60/min to 75/min. CO moderately increased, little change in CVV and LAtP. However, the resetting in MAoP results in a large Sy and CO increase. Heart rate is further increased (90/min). In steady state conditions of exercise the AoP and pulse amplitude are increased, MAoP about 108 mm Hg, CO almost doubled, LAtP slightly decreased, heart rate 75/min. Exhaustion of LV sympathetic drive (Sy decrease) and mild LV failure result in a AoP and MAoP decrease and a large LAtP increase. Heart rate is increased, CO is below exercise level, but above resting state level.

Fig. 2C shows the time course of cardiovascular variables (i.e. AoP, MAoP, LVP, LAtP, EDVLV, ESVLV and SVLV) during systole and part of diastole after aortic stenosis (93.7 s - 94.3 s). Note a relatively large aorto-ventricular pressure gradient. LAtP and EDVLV are slightly increased and ICT decreased. Aortic flow is evenly distributed through mid- and late systole. Fig. 2B is identical to Fig. 1B and is displayed together with Fig. 2C to illustrate the changes during aortic stenosis.

The changes in AoP, MAoP, LVP, LAtP, EDVLV, ESVLV and SVLV values induced by exercise in aortic stenosis are shown in Fig. 2D. The aorto-ventricular gradient is further increased. Due to vigorous LV contraction ICT is strongly decreased, therefore the peak of aortic flow occurs early in systole. Consequently, LAtP is slightly decreased and in early diastole LVP becomes negative. The effect of exhaustion of sympathetic drive and mild LV failure is simulated in Fig. 2E. Note the persistence of the aorto-ventricular gradient. ICT is slightly lengthened and, consequently, aortic flow proceeds late in systole. LAtP and EDVLV are increased.

4. Discussion

4.1 General comments

It should be pointed out that in present circuit i) a flow-dependent decrease in pulmonary vascular resistance is not simulated and ii) the control of peripheral (arteriolar) resistance is not included into the negative feedback. In principle it would be possible to include both features. However, this would considerably contribute to the complexity of the circuitry, without contributing very much to the understanding of underlying physiological mechanisms.

But despite the simplifications described above the negative feedback (incorporating the control of venous volume, of contractility of RV and LV, and of heart rate) seems to be quite similar to that controlling the human cardiovascular system (Berne & Levy, 1997; 1998; Germann & Stanfield, 2004; Guyton, 1966; Guyton et al., 1973; Guyton & Hall, 1996; Kusumoto, 2000).

4.2 Specific comments

It is well known that in man the resting MAoP can be reset from the normal to a higher level and then maintained by homeostatic mechanisms until required (e.g. in increased sympathetic tone, as a conditioned reflex before exercise, or during exercise; (Berne & Levy; 1997; Topham & Warner, 1967)). The resetting mechanism should include procedures whereby the resting MAoP, "clamped" at about 98 mm Hg is shifted and then "clamped" again at a higher level.

If MAoP is reset the main change is a temporary increase in heart rate and a moderate, steady state increase in CO and very slight decrease in CVV (Fig. 1A). Compared with resting conditions (MAoP about 98 mm Hg) it is clear that the increase of MAoP (to about 120 mm Hg) is due to a combination of slight venoconstriction and increased force of contraction of left ventricle (decreased early diastolic pressures, decreased EDVLV, strongly increased SVLV and its ejection fraction; Fig. 1B).

Animal experiments showed that in exercise the initiating factor is a decrease in peripheral resistance in working muscles, therefore MAoP is decreased. Consequently, through homeostatic mechanisms cardiac output is increased and MAoP reset to a higher level (Topham & Warner, 1967).
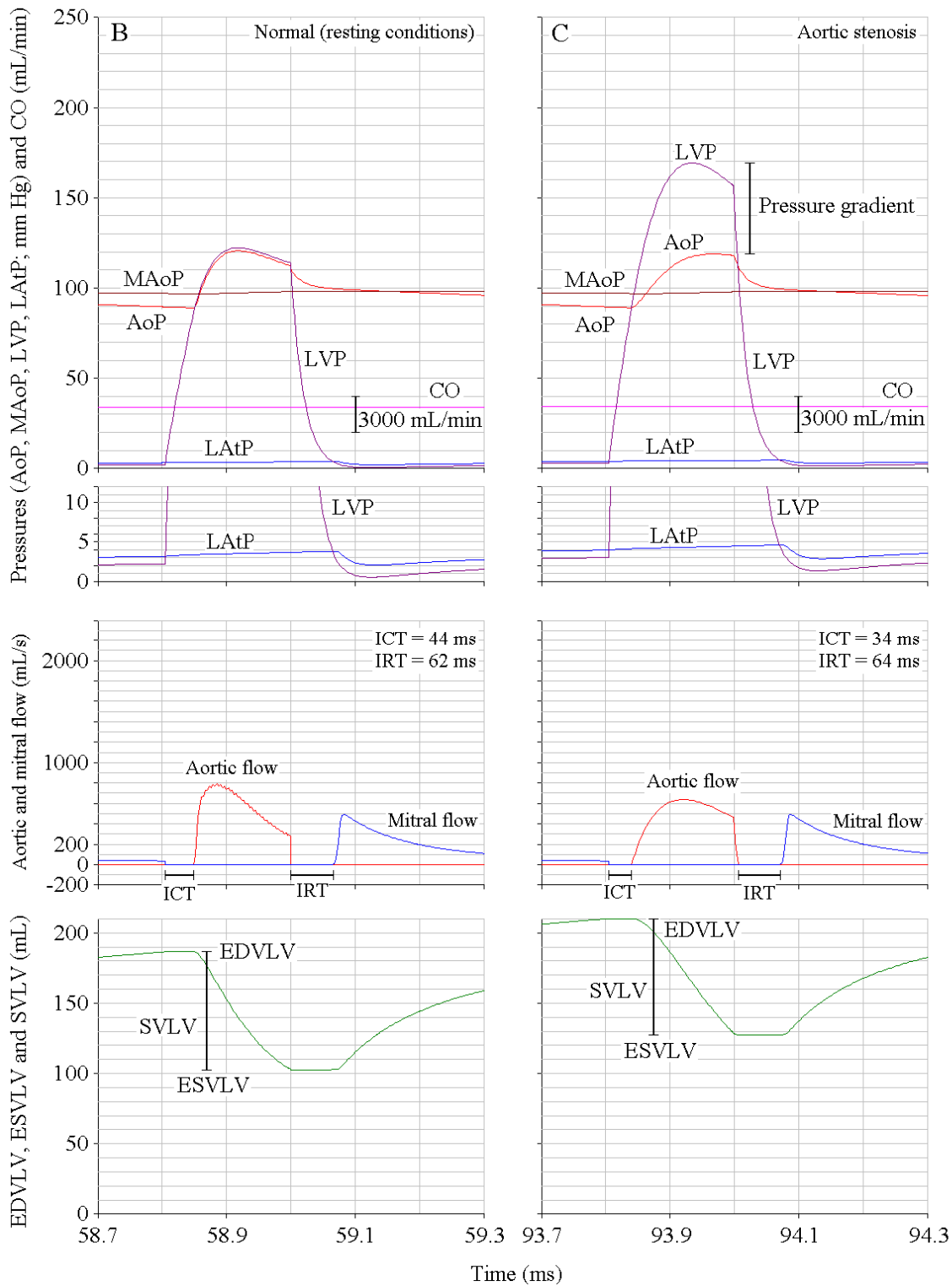
Fig. 2B, C: AoP, MAoP, LVP, LAtP, CO (upper two blocks), aortic and mitral flow (middle block), and left ventricular volumes (bottom block) recorded during systole and part of diastole. B: Normal (resting) conditions (58.7 s - 59.3 s). Note the peak aortic flow in mid-systole and peak mitral flow in early diastole. C: Aortic stenosis (93.7 s - 94.3 s). Note a pressure gradient (about 50 mm Hg) between AoP and LVP. A slight LAtP and EDVLV increase and ICT decrease. Peak aortic flow is shifted to late systole.
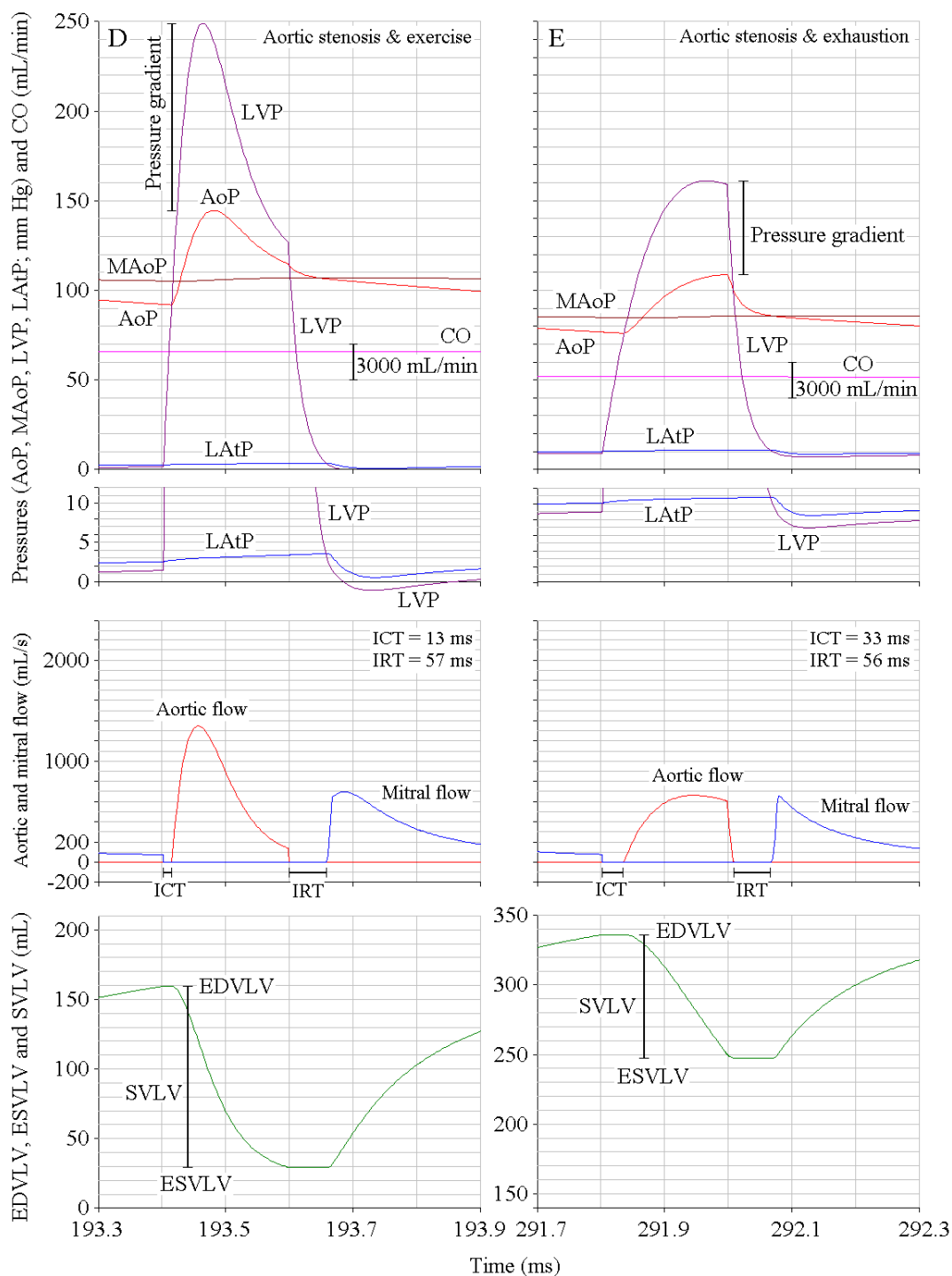
Fig. 2D, E: AoP, MAoP, LVP, LAtP, CO (upper two blocks), aortic and mitral flow (middle block), and left ventricular volumes (bottom block) recorded during systole and part of diastole. D: Aortic stenosis and exercise (193.3 s - 193.9 s). Note a huge pressure gradient (about 100 mm Hg) between AoP and LVP. Due to a vigorous LV contraction ICT is further decreased; peak aortic flow in about mid-systole. Early diastolic LVP slightly negative. E: Aortic stenosis, exhaustion and mild LV failure (291.7 s - 292.3 s). The pressure gradient (about 50 mm Hg) persists. Note a strong LAtP and EDVLV increase. Peak aortic flow is in late systole.

In this investigation exercise is simulated by decreasing arteriolar and capillary resistance by 50 % and by resetting MAoP (Fig. 1A, B, C). Transient phenomena in these variables are over in about 30 s. Steady state conditions are established where AoP, MAoP, CO and heart rate are about 160/92 mm Hg, 108 mm Hg, 9930 ml/min and 75/min, respectively. Strongly decreased CVV and slightly decreased LAtP. The time course of AoP, MAoP, LVP, LAtP, CO and SVLV during the early part of the heart cycle are shown in Fig. 1B, C. Compared to resting conditions the force and rate of contraction of left ventricle is highly increased, thus increasing SVLV and its ejection fraction. Qualitatively, simulation results described are quite similar to those obtained in experimental animal (Topham & Warner, 1967). Quantitatively, compared to simulation, the main dissimilarity is the fact that in experimental animal and man in exercise the range of heart rate is large, about 60/min to 180/min (Topham & Warner, 1967; Berne & Levy, 1997). In this simulation the range of heart rate is much less (60/min - 75/min - 90/min); in steady state conditions heart rate is 75/min. If the range of heart rate is increased (60/min - 90/min - 120/min) in steady state conditions heart rate is 90/min. However, results are similar in both heart rate settings (cf. also Table 1). In steady state conditions AoP, MAoP, CO and heart rate are about 150/95 mm Hg, 109 mm Hg, 10100 ml/min and 90/min, respectively. This is because in this model the heart rate/cardiac output curve is very flat, as shown earlier (Podnar et al., 2002); an increase in heart rate from 90/min to 120/min results in a comparatively small increase in CO.

At rest + aortic stenosis				
HR	LVP	MAoP	AoP	CO
in steady state conditions				
min^{-1}	(mm Hg)			ml/min
60	170/3	98	118/90	5145

Exercise + aortic stenosis					
HR		LVP	MAoP	AoP	CO
Maximum during transient	in steady state conditions				
min^{-1}	min^{-1}	(mm Hg)			ml/min
90	75	248/1.5	106	145/92	9900
120	90	220/1.0	108	137/95	10125

Table 1. The effect of aortic stenosis (at rest and in exercise) on heart rate (HR), pressure in the left ventricle (LVP: ventricular maximum/end-distolic), mean aortic pressure (MAoP), aortic pressure (systolic/diastolic; AoP) and cardiac output (CO).

Aortic stenosis is a chronic disturbance compensated by long-term cardiovascular control mechanisms. Clinically, it can be subdivided into valvular, subvalvular, and supravalvular variant. However, for a successful simulation of these variants additional data - on magnitude and on the distribution – of resistance and elastance (capacitance) would be required. As they are not available, present simulations apply to the valvular variant of aortic stenosis only.

If the patient featuring aortic stenosis is exercised the short-term control mechanisms are invoked. Thus, it would be of interest to make use of the present equivalent electronic circuit, to modify it according to this pathology. Data obtained by simulation could be compared with data obtained in clinical examination in man. A similarity in results could show a wider applicability of analogue simulation and possibly contribute to the understanding of homeostasis in this particular situation. In man, the effect of aortic stenosis on cardiovascular variables was studied at rest, in exercise and in conditions of pharmacologically induced decreased peripheral resistance (Anderson et al., 1969; Arshad et al., 2004; Bache et al., 1971; Diver et al., 1988; Huber et al. 1981; Peterson et al., 1978; Vanoverschelde et al., 1992).

Simulation of this clinical condition is shown in Fig. 2A. On increasing aortic resistance only a transient, small decrease in AoP shows up. Shortly afterwards exercise (decrease in peripheral resistance) results in a decrease in AoP and MAoP and increase in heart rate to 75/min. However, as soon as MAoP is reset heart rate is further increased to 90/min. Consequently, AoP and pulse amplitude increase. In steady state conditions heart rate is 75/min, AoP and MAoP are about 145/92 mm Hg and 106 mm Hg, respectively. CO is almost doubled, CVV strongly and LAtP slightly decreased. However, as soon as the sympathetic drive is decreased and mild LV failure induced, CO is decreased and LAtP strongly increased.

The time course of AoP, MAoP, LVP, LAtP, CO and SVLV during the early part of a heart cycle is shown for normal conditions in Fig. 2B and for aortic stenosis in Fig. 2C. It results in an increased force and velocity of contraction of left ventricle. This is shown by a decrease in ICT. The ventriculo-aortic pressure gradient is about 50 mm Hg. Because LAtP is slightly increased, EDVLV is slightly increased and CO is almost normal. Note that aortic stenosis results in a slower time course of aortic flow.

If in this condition peripheral resistance is decreased and MAoP reset (Fig. 2D) the ventriculo-aortic pressure gradient is increased to almost 100 mm Hg. LAtP is almost normal, EDLVL decreased and its ejection fraction strongly increased. Aortic flow is increased, but featuring a much slower time course.

Data obtained in patients (Anderson et al., 1969; Bache et al., 1971; Diver et al., 1988; Huber et al. 1981; Peterson et al., 1978; Vanoverschelde et al., 1992) showed that in some patients exercise resulted in a large, while in other patients in a very small increase in heart rate. It would be thus of interest to asses - at the same aortic resistance - the effect of heart rate on the ventriculo-aortic pressure gradient, aortic pressure and pulse pressure. Therefore, beside the frequency range 60/min, 75/min and 90/min another simulation is performed in which range of frequencies 60/min, 90/min and 120/min is used. Data obtained in steady state conditions and during transient phenomenon are summarised in Table 1.

Ventriculo-aortic pressure gradient, aortic pressure, pulse pressure and cardiac output are affected by heart rate, but differences are relatively small.

Investigations on aortic stenosis in patients showed that the average left ventricular end-diastolic pressure (LVEDP) was 12 mm Hg at rest and 20 mm Hg in exercise (Bache et al., 1971). But individual patient data showed that LVEDP at rest may have been quite low (3 mm Hg; Anderson et al., 1969). This is very close to that LVEDP recorded in simulations above. However, almost as a rule, in exercising patients LVEDP regularly increased (7 mm Hg; Anderson et al., 1969) in some patients quite high, 36 mm Hg (Bache et al., 1971) or even 41 mm Hg (Anderson et al., 1969). In simulations however, in aortic stenosis and exercise

LVEDP does not change or is slightly decreased. In explaining this simulation phenomenon it should be remembered that LVEDP is a variable depending on various (homeostatically controlled) parameters. If in exercise predominantly the contractility of LV is increased, LVEDP tends to decrease. On the contrary, if in exercise venoconstriction predominates, LVEDP will tend to increase. In patients with aortic stenosis in exercise the latter compensatory mechanism is more likely to occur.

It is clear that simulation data agree well - qualitatively, sometimes even quantitatively - with data obtained in patients (Anderson et al., 1969; Bache et al., 1971; Diver et al., 1988; Huber et al. 1981; Peterson et al., 1978; Vanoverschelde et al., 1992) or in patients with hypertrophic cardiomyopathy and outflow tract gradient (Geske et al., 2007, 2009; Sorajja et al. 2008).

Exhaustion of LV sympathethetic drive and mild LV failure is simulated in Fig. 2A and 2D. As expected, the aorto-ventricular gradient persists and pulmonary congestion is quite pronounced. EDVLV is increased and aortic flow with a very slow time course. It seems that these changes contribute to the understanding of homeostasis and its failure in exercise, the syncope, a frequent complication.

5. Conclusions

A computer analysis of an equivalent electronic circuit is developed to simulate the human cardiovascular system and its homeostatic control. Thus the response of the system can be studied if the latter is acted upon by various disturbances. In present simulation these are

- exercise in normal conditions and
- exercise in a subject featuring aortic stenosis, including exhaustion of compensatory mechanisms.

Exercise is simulated by a decrease in peripheral resistance and by an increase in sympathetic tone (resetting the mean aortic pressure to a higher level).

In exercise in normal conditions, through negative feedback, cardiac output, systolic aortic pressure, force and frequency of left ventricle contraction, are increased. The time course of aortic flow reflects changes of left ventricle contraction dynamics. Mean aortic pressure is mildly increased. There is almost no change in diastolic aortic pressure.

In exercise in aortic stenosis, through negative feedback, similar changes occur as described above. However, in these conditions the dominant feature is a large aorto-ventricular pressure gradient, almost doubling the systolic left ventricular pressure. It can be assumed that the latter results in an exhaustion of sympathetic (inotropic) mechanism(s). The final result is a decrease in aortic pressure, a sluggish aortic flow and pulmonary congestion.

It seems that consequences of i) exercise and ii) exercise in aortic stenosis can be qualitatively successfully simulated (resembling actual clinical conditions), including an exhaustion of compensatory mechanisms. Quantitatively, however, there are minor differences, because many quantitative data on human cardiovascular system are still lacking.

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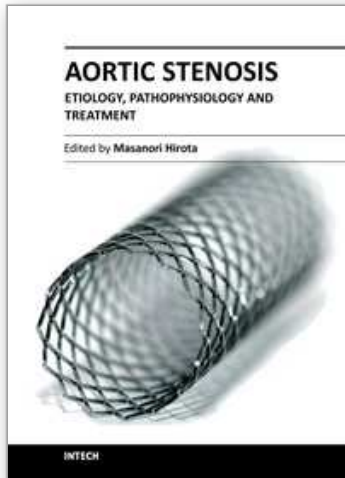
Aortic Stenosis - Etiology, Pathophysiology and Treatment

Edited by Dr. Masanori Hirota

Currently, aortic stenosis (AS) is the most prevalent valvular disease in developed countries. Pathological and molecular mechanisms of AS have been investigated in many aspects. And new therapeutic devices such as transcatheter aortic valve implantation have been developed as a less invasive treatment for high-risk patients. Due to advanced prevalent age of AS, further discovery and technology are required to treat elderly patients for longer life expectancy. This book is an effort to present an up-to-date account of existing knowledge, involving recent development in this field. Various opinion leaders described details of established knowledge or newly recognized advances associated with diagnosis, treatment and mechanism. Thus, this book will enable close intercommunication to another field and collaboration technology for new devices. We hope that it will be an important source, not only for clinicians, but also for general practitioners, contributing to development of better therapeutic adjuncts in the future.

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