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The effect of hemodilution on regional myocardial function in the presence of coronary stenosis*)

Isovolumische Hämodilution bei eingeschränkter Koronarreserve: Wirkung auf die globale und regionale Myokardfunktion

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With 11 figures and 1 table

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Summary

Hemodilution decreases blood viscosity and circulatory input impedance and thus reduces afterload. Its use in treatment of LV power failure has been advocated, but the safe limits of isovolemic hemodilution are not known. Compensation of the reduced O_2-capacity of the blood was therefore studied with normal and impaired coronary reserve.

In 20 dogs the LAD was stenosed to a degree just not affecting the supplied region and central and coronary hemodynamics were studied. Regional myocardial function was assessed by ultrasound transit time between transducers implanted in the LV wall. Lowering the hematocrit to 15 % by isovolumic exchange of blood for Dextran 60 increased CVP (18 %), PAP (47 %), LAP (64 %), LVedP (46 %), CO (67 %), and flow to the intact area (LCA: 211 %). Flow in the stenosed LAD increased slightly. Enddiastolic length (EDL) of LAD dependent muscle segments rose to 120 % and their contraction amplitude ΔL was decreased by 46 %. Whereas non-ischemic segments showed compensatory rise in ΔL (38 %) at almost constant EDL (+ 9 %). After release of the LAD stenosis EDL and ΔL returned to normal.

During progressive anemia myocardial O_2-demand is not adequately met if coronary reserve capacity is depleted. Reversion of hypokinesia after removal of the stenosis shows unimpaired myocardial function at a hematocrit as low as 15 % provided the coronary circulation is intact.

Several studies have demonstrated that acute limited isovolumic hemodilution does not impair myocardial function in hearts with intact coronary circulation (2, 4, 7, 8, 9, 13, 16, 19, 24). The reduced arterial oxygen content of the diluted blood is compensated for by an excessive

*) Mit Unterstützung des Sonderforschungsbereichs 37.

preferential increase in coronary flow (18, 30) caused by reactive coronary vasodilation and the improvement of blood fluidity. The decrease of blood viscosity lowers aortic input impedance and therefore reduces external heart work. In addition, the oxygen transport capacity reaches its maximum at a hematocrit level of about 30 % under the condition of improved microcirculation (28). These mechanisms are suggested to be responsible for covering the oxygen demand of the heart during anemia. A limited compensatory increase in oxygen extraction is quantitatively less important (25).

These compensatory mechanisms however may fail in hearts where the functional coronary reserve capacity is limited or depleted. This question has gained importance in heart surgery, especially in the surgical treatment of coronary artery and cyanotic heart disease where acute hemodilution during extracorporeal circulation is widely used to overcome the known disadvantages of blood primes.

On the other hand, hemodilution with concomitant decrease in afterload and improvement of microcirculation may be considered as a concept in the treatment of left ventricular power failure. From studies in the infarcted dog heart, *Yoshikawa* and coworkers (32) concluded that in response to hemodilution collateral coronary circulation and oxygen delivery to the infarcted area is improved. From these findings, one may suggest that hemodilution can be used in myocardial infarction to lower the high blood viscosity observed in these states (6), to improve coronary collateral circulation and microcirculation and reduce afterload by improving blood fluidity.

These considerations however are valid only under the presumption of sufficient oxygen supply to cover the demands of the heart. The following experiments were designed to investigate the effects of isovolumic hemodilution with dextran 60[1]) on total and regional myocardial function in hearts with intact coronary circulation and in the myocardium where coronary reserve is already limited respectively depleted.

Methods

I. Preparation and monitored parameters (fig. 1)

20 mongrel dogs (23.7 ± 1.8 kg) were anesthetized with sodium pentobarbital[2]) (20 mg/kg) and continuous infusion of piritramide[3]) (0.001 mg/min · kg). The animals were ventilated by a respirator (Servoventilator 900)[4]) with 50 % oxygen.

To prevent atelectasis PEEP was set at 7 cm H_2O. A left thoracotomy was performed in the 5th intercostal space and the heart exposed and suspended in a pericardial cradle. The left anterior descending (LAD) and the left circumflex artery (LCA) were dissected free near the origin for placement of ultrasonic flow probes.

The coronary flows $\dot{Q}_{LAD}$ and $\dot{Q}_{LAC}$ were measured by a pulsed Doppler ultrasonic flowmeter[5]) (22). Cardiac output was monitored by an electromagnetic

[1]) Macrodex 6 %, Knoll AG, Ludwigshafen, W. Germany
[2]) Nembutal, Deutsche Abbott GmbH, Ingelheim a. Rhein, W. Germany
[3]) Dipidolor, Janssen Pharmaceutica, Beerse, Belgium
[4]) Elema-Schönander, Stockholm, Sweden
[5]) Roche Bioelectronics, Paris, France

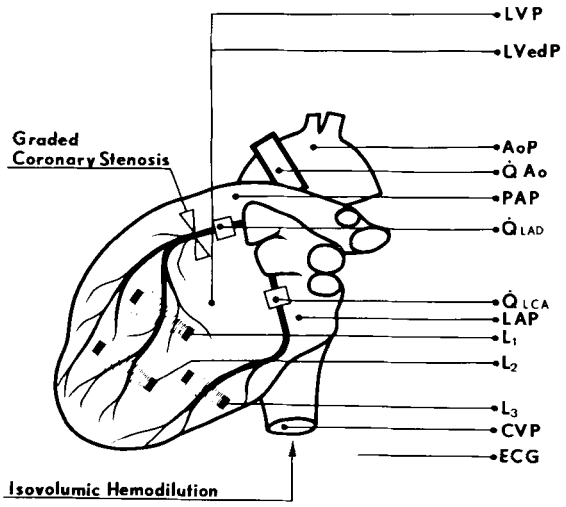

Fig. 1. Schematic representation of the experimental preparation of the dog heart (for details see the text).

flowmeter (Statham SP 2202)[6]) around the ascending aorta. Left ventricular pressure (LVP), left ventricular enddiastolic pressure (LVedP), and aortic pressure (AoP) were measured by a double catheter tip manometer (Millar Micro-Tip PC 771)[7]) via the left carotid artery. Polyethylene catheters were placed in the right atrium (RA), the pulmonary artery (PA), and the left atrium (LA) and connected to Statham P23Db[8]) pressure transducers to monitor CVP, PAP and LAP. dP/dt_{max} was calculated from the online differentiated LVP signal (Brush Differentiator)[9]). All parameters were continuously recorded on a multichannel Brush recorder (Brush 481)[9]) and on a magnetic tape (Siemens Meditape 12)[10]). (dP/dt): IP (31) used as a contractile index was obtained from high speed recordings (200 mm/s). The mean data as heart rate (HR from ECG), mCVP, mPAP, mLAP, mAoP, CO, Q_{LAD}, Q_{LCA}, and rectal temperature were collected in 30 seconds intervals by a computer (Siemens 404/3 System Simon)[10]). Blood samples were taken before every data collecting period from the aorta and central venous system to measure pH, P_{O_2}, P_{CO_2}, HCO_3, BE, hemoglobin, hematocrit, and potassium. Electrolyte and fluid balance was maintained by infusion of Ringer's solution[11]).

II. Regional myocardial function

The technique used to obtain continuous measurements of regional myocardial function was developed by *Bugge-Asperheim* in 1969 (3) and independently by *D. Franklin* and associates (10) and is based on ultrasonic transit time measurement. In own studies (12, 14) this method was shown to be a reliable tool for continuous measurement of myocardial segment dimensions. Couples of 5 MHz

[6]) Statham Instruments Inc., Oxnard, USA
[7]) Millar Instruments Inc., Houston, USA
[8]) Statham Instruments Inc., Hato Rey, Puerto Rico
[9]) Gould Brush Inc., Cleveland, USA
[10]) Siemens AG., Erlangen, W. Germany
[11]) Delta-Pharma, Klemenz u. Co., Pfullingen, W. Germany

miniaturized piezoelectric crystals with a diameter of about 1.5 to 2 mm were implanted into the myocardial wall defining muscle segments in a certain depth and along a certain contraction vector. The emitter crystal (lead-titanate-zirconate) is excited by a 10 ns 180 volt pulse. The resonance oscillation abates very quickly and therefore very short distances can be measured (min. 2 mm). The emitted longitudinal ultrasound wavefront travels through the myocardium with a constant velocity of 1.56 mm/μs and bounds against the receiver crystal (after a certain transit time) exciting it to oscillate with its natural frequency. To guarantee that the ultrasound beam meets the receiver during the movement of the myocardial wall, the acoustic field was extended by moulding hemispherical polystyrene lenses onto the piezoelectric discs. The received ultrasound is transferred to an electrical signal. In the receiver circuit a constant current is integrated from the moment of emission until the receiver crystal is excited. The resultant integral reflects the instantaneous distance of the crystals. A repetition rate of 1 kHz provides a continuous measurement of dynamic changes of myocardial segment dimensions with a high frequency response. The dynamic recording of changes in segment dimensions is obtained from the difference between maximal and minimal ultrasound transit time. The measured transit time is calibrated in steps of 1 μs generated by an accurate quartz-controlled oscillator (fig 2).

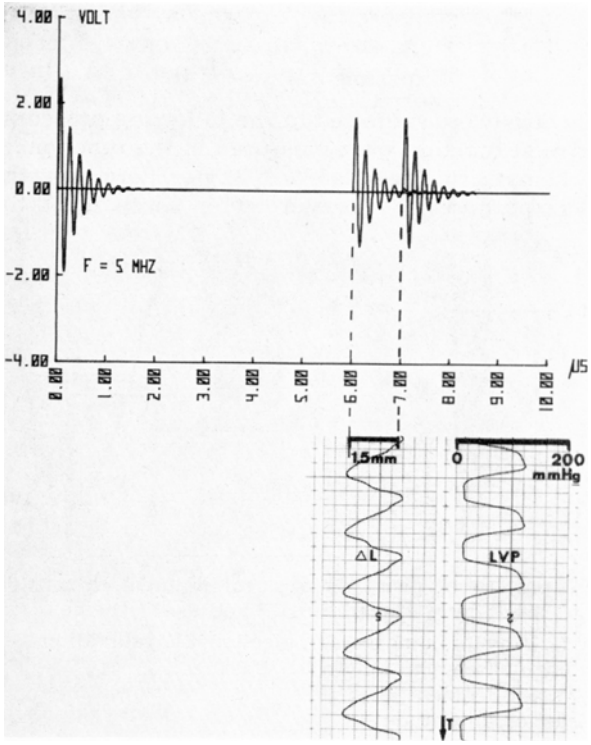

Fig. 2. Principle of the ultrasonic transit-time method for direct measurement of myocardial segment dimensions. Dynamic recording of phasic segment-length changes (ΔL) is obtained from the difference between maximal and minimal transit-time of ultrasound (for details see the text).

Three couples of crystals were implanted into the myocardium 15 to 30 mm apart parallel to the minor axis of the left ventricle in the following positions (compare fig. 1):

1. Two pairs of transducers in a subendocardial respectively epicardial muscle layer in the anterior wall supplied by the LAD.
2. A third couple in a subendocardial layer of the posterior wall supplied by the LCA.

The normal pattern of myocardial segment dynamics in relation to LVP and AoP is shown in figure 3 as it is obtained by this method. During the initial filling (I) segment length increases rapidly reaching its maximum with atrial contraction. With increasing tension during the isovolumic phase (II) segmental length slightly decreases caused by changes in geometry of the total left ventricle during this period. After aortic valve opening (ejection: III) the segment shortens with almost constant velocity. During relaxation further shortening occurres along the minor axis related to the changes of left ventricular shape.

From these curves the following parameters can be obtained:

1. the enddiastolic length (EDL), 2. the endsystolic length (ESL), 3. the contraction amplitude (ΔL), and 4. the velocity of shortening (dL/dt).

EDL and ΔL are used to describe regional myocardial function in the following. The pressure-length-loop generated from the signals shown below illustrates even better the above described relation between LVP and segment length (compare fig. 3b).

Experimental procedure

A total of 20 dogs were subjected to the following procedure: Total and regional myocardial function were measured in the functional steady state at the initial hematocrit level (45 % ± 3 %). Thereupon the LAD was mechanically compromised by a micrometer snare until the segmental

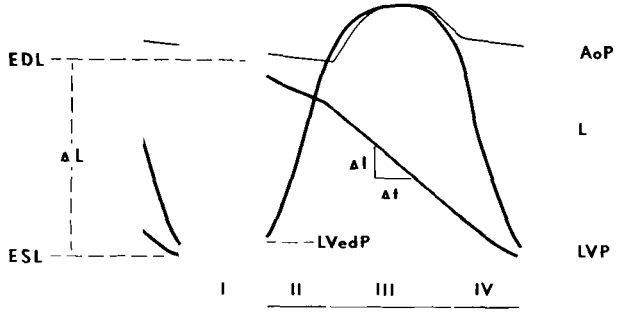

Fig. 3a. Normal pattern of phasic changes of segment dimensions during the heart cycle related to LVP and AoP (scheme).

I. filling-phase, II. isovolumic phase, III. ejection, IV. relaxation
EDL = enddiastolic segment length
ESL = endsystolic segment length
ΔL = contraction amplitude
Δl/Δt = velocity of segment shortening
LVedP = left ventricular enddiastolic pressure
LVP = left ventricular pressure
AoP = aortic pressure
(For explanation see the text.)

function in the dependent myocardial area was significantly disturbed. Subsequently the micrometer was released for 0.1 mm in circumference insuring that segmental function came back to the control level. After recording, stepwise (5 % Hct steps) hemodilution was performed by continuous blood dextran 60 (37 °C) exchange according to the method of *Messmer* et al. (17). The dogs were bled via a 3 mm cannula placed in the femoral artery. Infusion was performed via a 5 mm cannula inserted into the femoral vein. Ten to 15 minutes after every hemodilution step and after blood gas control data were collected during functional steady state condition. Hemodilution was stopped when local function was depressed to about 50 % of the initial value. The stenosis was then removed and after a recovery interval of 20 minutes the measurements were repeated. By this method every heart served as its own control. In 10 dogs stepwise hemodilution was continued after removal of the stenosis until segmental function was significantly depressed.

Results

A. Influence of isovolumic hemodilution on total cardiac function during "subcritical" LAD-stenosis

The general effects of progressive isovolumic anemia, induced by continuous blood dextran 60 exchange on myocardial performance are shown in figure 4. At a hematocrit of 45 % the mean values were: LVedP 8.3 ± 1 mm Hg, LVP 118 ± 7 mm Hg, diastolic AoP 89 ± 7.7 mm Hg, CO 2.1 ± 0.2 l/min. With progressive hemodilution LVedP and CO

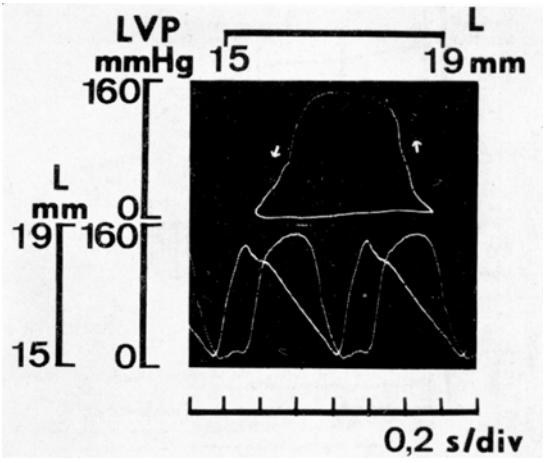

Fig. 3b. Normal pattern of phasic changes of segment dimensions during the heart cycle related to LVP (original tracings).

LVP = left ventricular pressure
L = segment length
lower panel: dynamics of a subendocardial muscle segment (parallel to the minor heart axis) and LVP
upper panel: left ventricular pressure-length loop generated from the signals shown below

increased continuously and reached 12.1 ± 1.4 mm Hg (+ 46 %, $p < 0.05$) respectively 3.5 ± 0.6 l/min (+ 67 %, $p < 0.05$) at 15 % hematocrit. LVP and diastolic AoP decreased by −3 % and −13 % ($p > 0.05$). After removal of coronary stenosis LVedP, LVP, and diastolic AoP fell, but cardiac output rose. These changes however were not significant (compare table 1). The influence of hemodilution on HR, CVP, PAP, LAP, dP/dt, and (dP/dt): IP are summarized in table 1. Lowering hematocrit from 45 % to 15 % induced an increase in PAP (+ 47 %, $p < 0.05$), in LAP (+ 64 %, $p > 0.05$), in dP/dt_{max} (± 3 %, $p > 0.05$), and in (dP/dt): IP (+ 32 %, $p > 0.05$). The velocity of left ventricular relaxation fell continuously from 1790 mm Hg/s to 1376 (−23 %, $p > 0.05$). HR and CVP did not significantly change (compare table 1). In response to coronary flow restoration no significant changes of these parameters were observed.

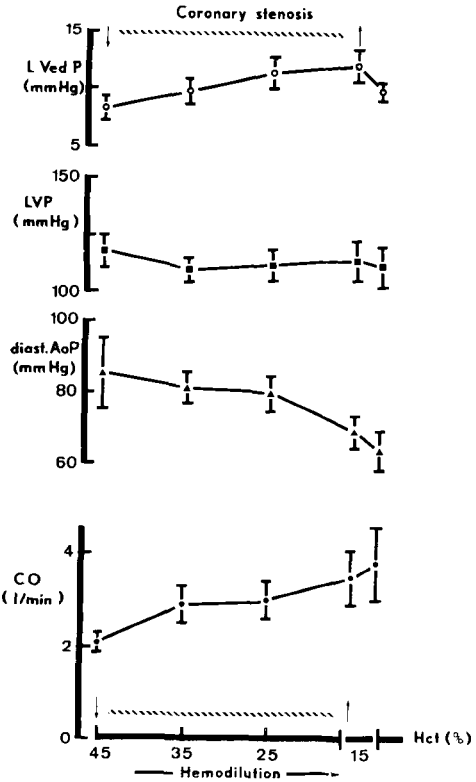

Fig. 4. Effects of hemodilution on total left ventricular function during "subcritical" LAD stenosis.

LVedP = Left ventricular enddiastolic pressure
LVP = left ventricular pressure
diast. AoP = diastolic aortic pressure
CO = cardiac output
(values are expressed as mean ± SEM)
LAD stenosis was removed at 15 % Hct.

Table 1. Summarized effects of isovolumic hemodilution in hearts with singular coronary stenosis on total and regional myocardial function.

Hct	%	45	35	25	15	15
Stenosis		+	+	+	+	–
HR	1/min	110 ± 7.4	109 ± 5.8	115 ± 8.5	120 ± 10	117 ± 14
CVP	mm Hg	4.0 ± 1.1	4.3 ± 0.5	4.3 ± 0.6	4.7 ± 0.7	4.2 ± 0.7
PAP	mm Hg	10.3 ± 0.7	11.8 ± 0.3	13.5 ± 0.9	15.1 ± 0.8*	14.9 ± 0.9
LAP	mm Hg	4.7 ± 1.4	5.3 ± 1.1	6.6 ± 1.2	7.7 ± 1.4	6.4 ± 0.7
LVedP	mm Hg	8.3 ± 1.0	9.8 ± 1.1	11.4 ± 1.4	12.1 ± 1.4*	9.9 ± 0.8
LVP	mm Hg	118 ± 7.0	110 ± 5.2	112 ± 7.1	114 ± 8.7	111 ± 8.7
AoP diast	mm Hg	89 ± 7.7	86 ± 3.3	85 ± 3.7	77 ± 3.5	73 ± 4.1
dP/dt_{max}	mm Hg/s (+)	1645 ± 403	1867 ± 149	1884 ± 137	2155 ± 197	2503 ± 167
dP/dt_{min}	mm Hg/s (−)	1790 ± 130	1810 ± 159	1778 ± 164	1376 ± 262	1725 ± 45
(dP/dt): IP	1/s	21.6 ± 3.7	23.0 ± 1.8	25.5 ± 2.5	28.5 ± 2.4	28.1 ± 3.2
CO	l/min	2.1 ± 0.2	2.9 ± 0.4	3.0 ± 0.4	3.5 ± 0.6*	3.8 ± 0.8
$\dot{Q}_{LCA}$	ml/min	90	125	230	280	275
EDL_3	%	100	103.0 ± 1.3	103.9 ± 4.4	109.0 ± 1.9*	103.4 ± 4.1
ΔL_3	%	100	120.4 ± 7.0	128.3 ± 10.7	138.4 ± 17.4*	129.6 ± 8.4
$\dot{Q}_{LAD}$	ml/min	68 ± 10	73 ± 8.2	69 ± 9.1	100 ± 10.7*	192 ± 23*
EDL_{1+2}	%	100	107.1 ± 1.7	114.2 ± 3.2	119.7 ± 3.2*	106.5 ± 2.5*
ΔL_{1+2}	%	100	81.3 ± 4.6	68.7 ± 7.5	54.1 ± 8.0*	93.5 ± 5.9*

EDL = enddiastolic segment length
ΔL = contraction amplitude
1 + 2 = muscle segments supplied by the stenosed LAD
3 = muscle segment supplied by the intact LCA
* = $p < 0.05$
Stenosis was removed at 15% hematocrit.
Values are expressed as mean ± SEM.
Significance (*Student* t-Test) of changes between Hct 45% and 15% was calculated.

B. Influence of increasing anemia on coronary flow

Figure 5 demonstrates the effects of progressive isovolumic hemodilution on coronary flow in the intact LCA and the mechanically compromised LAD. Prior to the placement of coronary stenosis the flow in the LAD averaged 68 ± 10 ml/min and 90 ml/min in the LCA. Q_{LAD} fell slightly to 68 ml/min in response to the placement of a "subcritical" stenosis and remained fairly constant over a wide range of hematocrit. At 15 % hematocrit Q_{LAD} reached 100 ± 10.7 ml/min which equals a 47 % increase ($p < 0.05$). In contrast, Q_{LCA} showed an early sharp increase in response to anemia and reached an excessive mean value of 280 ml/min at 15 % hematocrit (+ 211 %). After coronary stenosis was removed Q_{LAD} increased to 192 ± 23 ml/min (+ 182 %, $p < 0.05$) and remained constant at this level.

C. Influence of hemodilution on regional myocardial function:

I. in the myocardial area supplied by the intact LCA (fig. 6 B)

With progressive anemia the EDL increased slightly while ESL fell and subsequently ΔL rose. Lowering the hematocrit from 45 % to 15 % both EDL and ΔL increased significantly by 9 % respectively 38.4 % ($p < 0.05$). After restoration of coronary flow EDL and ΔL decreased. While EDL returned almost back to the initial range, ΔL remained distinctly elevated above the value found at 45 % hematocrit. These values are almost identical to those found in previous experiments, where

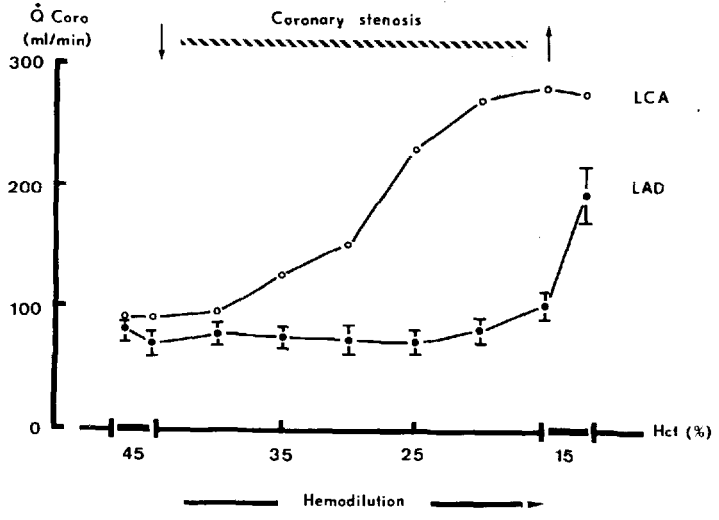

Fig. 5. Influence of isovolumic hemodilution on coronary flow.
LAD = left anterior descending artery (mechanically compromised)
LCA = left circumflex artery (intact)
LAD stenosis was removed at 15 Hct.
Values are expressed as mean ± SEM.
(For explanation see the text.)

hemodilution was performed in hearts with intact coronary circulation (compare fig. 6 A).

II. in the myocardial area supplied by the stenosed LAD (fig. 6 C)

In response to hemodilution from 45 % to 15 % subendocardial and epicardial segments showed a significant increase in EDL by 19.7 % ($p < 0.05$) of the initial value. The contraction amplitude ΔL decreased continuously with progressive anemia and averaged 54.1 % (−45.9 %, $p < 0.05$) of the initial value at a hematocrit of 15 %. No significant difference between the subendocardial and the epicardial segment in response to hemodilution was observed. After removal of LAD stenosis EDL fell from 119.7 % to 106.5 % and ΔL rose from 54.1 to 93.5 %. The induced changes were significant ($p < 0.05$).

The initial effects of removing the stenosis on the dynamics of the different segments at a hematocrit of 15 % are shown in figure 7. The decrease in EDL of all segments is clearly demonstrated. The ΔL increased in L_1 and L_2 in response to restored perfusion while the ΔL of the control segment L_3 decreased as described above.

Regional myocardial function at a low hematocrit and restricted coronary perfusion is characterized by a low performance of the affected segment as demonstrated. Besides these effects frequently local dysfunction was observed. Figure 8 shows an example. At a hematocrit of 15 %

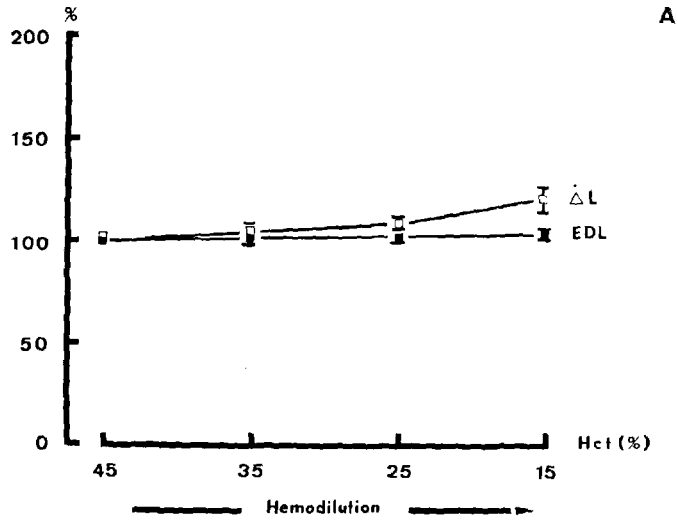

Fig. 6 a. Effects of progressive isovolumic hemodilution on regional myocardial function in hearts with intact coronary arteries.

Panel A: segment (subendocardial muscle layer) supplied by the *intact* LAD
EDL = enddiastolic segment length
ΔL = contraction amplitude
Values are expressed as mean ± SEM.
(For explanation see the text.)

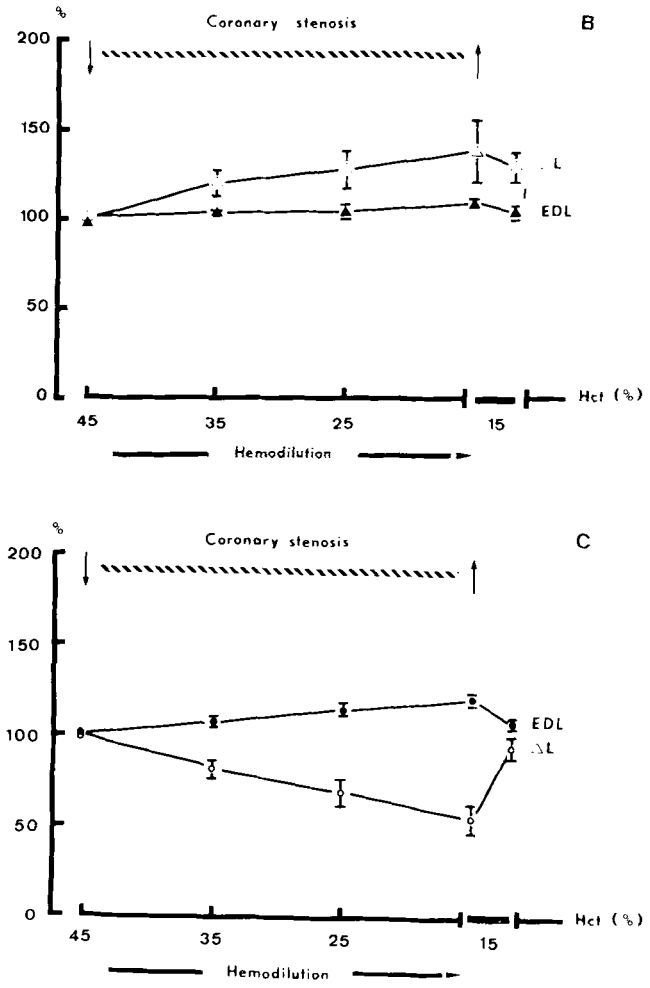

Fig. 6b. Effects of progressive isovolumic hemodilution on regional myocardial function during the presence of "subcritical" LAD stenosis.

Panel B: segment 3 (subendocardial muscle layer) depending on the *intact* LCA
Panel C: segment 1 and 2 (subendocardial and epicardial muscle layer) depending on the *restricted* LAD
EDL = enddiastolic segment length
ΔL = contraction amplitude
LAD stenosis was removed at 15 % hematocrit indicated by the arrow.
Values are expressed as mean ± SEM.
(For explanation see the text.)

L_1, even more pronounced L_2 showed disturbed function. The velocity of shortening and the contraction amplitude were markedly reduced. The main part of shortening occurred during ventricular relaxation. These changes are also visible in figure 7 (L_1 and L_2) before removal of the

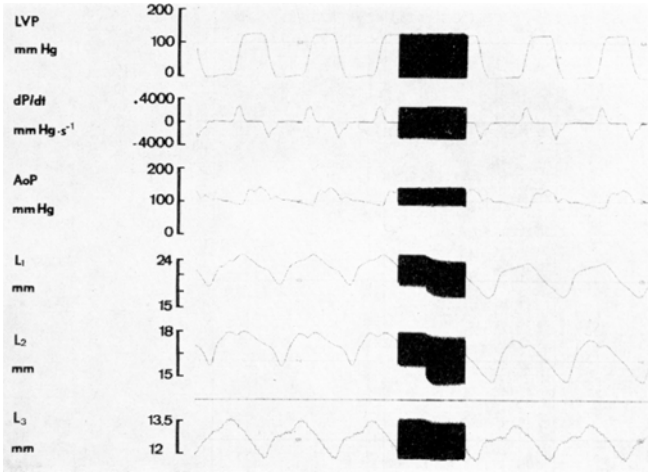

Fig. 7. Effect of removal of the stenosis on regional myocardial function at a hemotocrit of 15 % (original tracing).

LVP = left ventricular pressure
dP/dt = rate of left ventricular pressure rise
AoP = aortic pressure
L_1 = segment (subendocardial muscle layer) depending on restricted LAD
L_2 = segment (epicardial muscle layer) depending on restricted LAD
L_3 = segment (subendocardial muscle layer) depending on intact LCA
(For details see the text.)
(Recorder was stopped for 15 seconds during removal of the stenosis to prevent mechanical artefact on the chart.)

stenosis. Furthermore, mechanical alternans is generated in the myocardial region with restricted coronary perfusion while the intact segment showed normal function. After removal of coronary stenosis regional function improved immediately and the signs of dysfunction disappeared. In figure 9 an experiment is depicted where mechanical alternans appeared at 15 % hematocrit (9 A) in the area supplied by the restricted LAD ($L_1 + L_2$). After stenosis was removed the alternating pattern changed to regular contraction.

D. Influence of hemodilution on muscle distensibility in hearts with normal and restricted coronary perfusion

The general effects of hemodilution on regional myocardial distensibility and regional function are shown in figure 10.

In the upper panel LVedP is plotted versus EDL; in the lower LVP is plotted versus ESL.

In A hemodilution was performed in a heart with intact coronary circulation. With decreasing hematocrit from 45 to 12 % LVedP increased at fairly constant EDL demonstrating reduction in myocardial distensibility. In contrast, during the presence of coronary stenosis (C: $L_1 + L_2$) the slope of the pressure-length relation is flattened as observed during acute

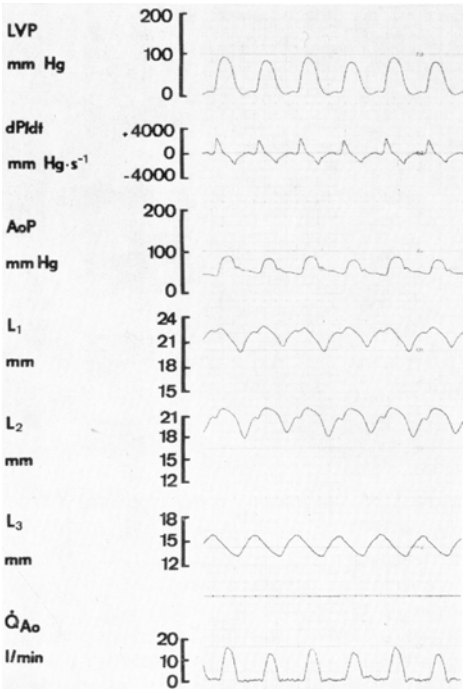

Fig. 8. Regional myocardial dysfunction (mechanical alternans, in L_1 and L_2 and ischemic bulging in L_2) in the area supplied by the stenotic LAD at a hematocrit level of 18 %. Normal contraction pattern in the region depending on the intact LCA (L_3).

LVP = left ventricular pressure
dP/dt = rate of left ventricular pressure rise
AoP = aortic pressure
QAo = aortic flow
(original tracing)
(For explanation see the text.)

ischemia. The control segment (B: L_3) in the same heart showed similar results as obtained in A. In response to perfusion at 15 % hematocrit the LVedP decreased in B and C, reaching the initial values. EDL of the control segment L_3 (B) decreased demonstrating reduced compliance in the low hematocrit state even after removal of the stenosis. The EDL of the previously underperfused segment (C) remained at a higher level compared to the initial value.

The ESL decreased with peak LVP in A but rose tremendously in C demonstrating the restriction of the functional capacity of the underperfused muscle area. In the control segment ESL remained unchanged with decreasing pLVP. With restoration of coronary flow ESL of the control segment (B) decreased while the segment in C remained unchanged as compared to the initial values.

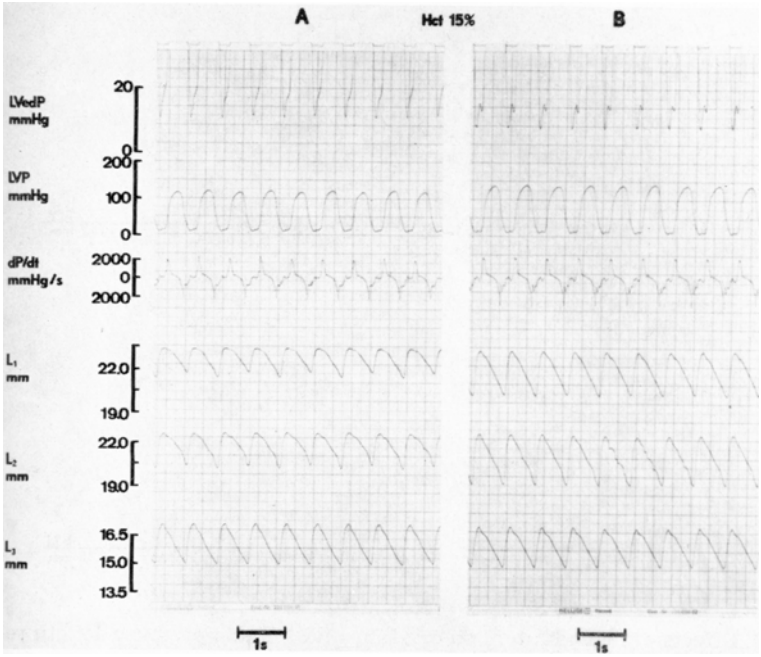

Fig. 9. Effect of coronary flow restoration on regional myocardial dysfunction at a hematocrit level of 15 %.

A = before, B: after removal of the stenosis
L_1 = subendocardial muscle segment (restricted LAD flow)
L_2 = epicardial musce segment (restricted LAD flow)
L_3 = subendocardial muscle segment (intact LCA flow)
(See the text for explanation.)

E. The effect of further hemodilution after removal of coronary stenosis

In 10 experiments hemodilution was continued after coronary stenosis was removed at a hematocrit level of 15 %. The EDL and ΔL remained fairly constant until a hematocrit of about 8 % was reached.

At this level depression of myocardial function with pronounced increase in EDL and marked decrease in ΔL appeared and became progressively impaired with further dilution. At 5 % hematocrit 50 % of the dogs died.

To detect masked limitation of myocardial function during the asymptomatic range between 15 % and 8 % hematocrit temporary total occlusion of the LAD was performed at 10 % hematocrit and the effects compared to those observed at hematocrit levels of 42 % and 19 % in the same heart. In response to coronary occlusion EDL and ESL immediately increased while ΔL fell markedly. During the occlusion period local dysfunction with paradoxical systolic expansion of the ischemic muscle occurred. After release of coronary occlusion immediate restoration of regional function was demonstrated at 42 % and 19 % hematocrit. At 10 % however recovery was markedly delayed and proceeded at a

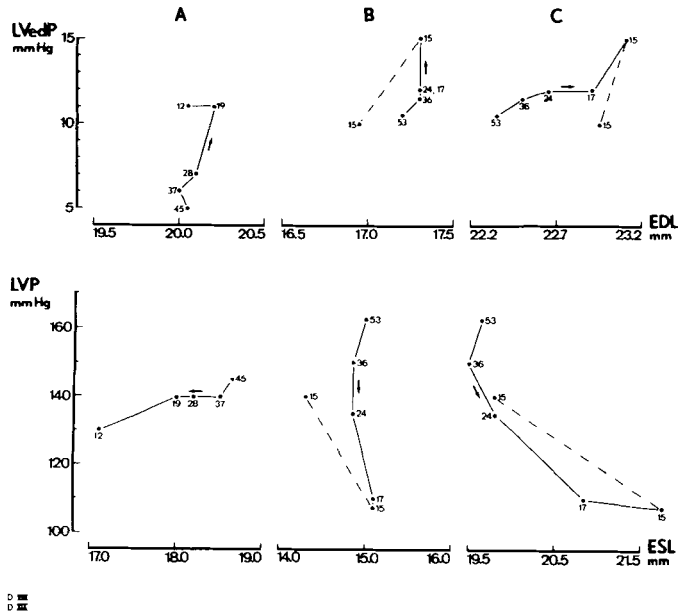

Fig. 10. Effects of hemodilution on diastolic and systolic pressure-length relationship

A = heart with intact coronary circulation
B = heart with restricted LAD flow (control segment supplied by intact LCA)
C = segment in the same heart as B but in an area supplied by the stenosed LAD
LVedP = left ventricular enddiastolic pressure
EDL = enddiastolic segment length
LVP = left ventricular pressure
ESL = endsystolic segment length
The numbers along curves indicate the hematocrit levels.
(For explanation see the text.)

distinctly slower rate indicating the marginal metabolic state at this hematocrit level.

Discussion

The present study considers the general effects of isovolumic hemodilution with dextran 60 on total and regional myocardial function in anaesthetized open-chest dogs with intact and restricted coronary circulation. The validity of the data given in this report depends to a great deal on the method used to evaluate regional myocardial function. The ultrasonic transit-time method was carefully examined in previous studies (12, 14). The maximal electronical error, induced by triggering dynamic signals with unstable amplitudes was calculated to 75 μm. The stability of measurements over hours and the repeatability of response to experimentally induced defined changes demonstrated the electronical and mechanical stability of the method. Furthermore the trauma to the myo-

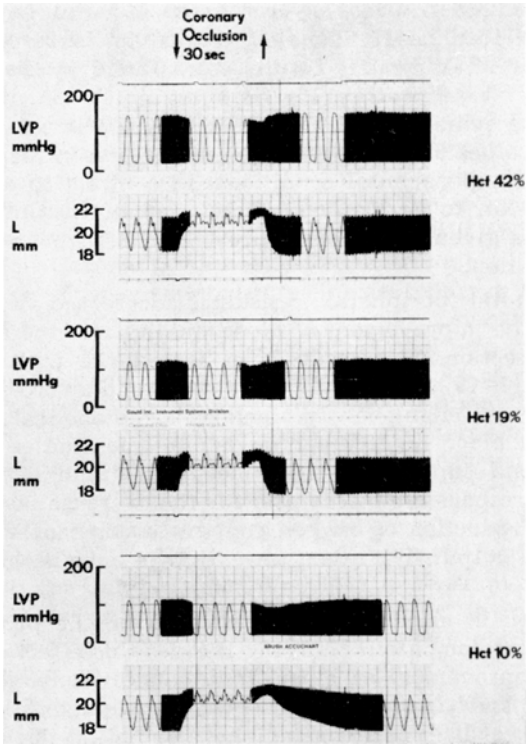

Fig. 11. Influence of different degrees of anemia (Hct 42 %, 19 % and 10 %) on the recovery time after temporary coronary occlusion in a heart with intact coronary arteries.
LVP = left ventricular segment
L = subendocardial muscle segment
(original tracing)
(For explanation see the text.)

cardium during implantation of the crystals is minimal as demonstrated by histological examination (29). Compared to other direct methods, the main advantage is the disconnection of the transducers from each other which highly reduces mechanical artefacts.

The method to produce graded coronary stenosis by using a micrometer snare led to fairly reproducible results in respect to coronary flow and regional myocardial function. The quantification of coronary stenosis is jeopardizing due to asymmetry narrowing of the coronary artery and changes in stenosis length. Therefore, the degree of coronary artery restriction to produce subcritical coronary stenosis was directly deduced from its effect on regional myocardial function, neglecting the percentage of the narrowing. From rough calculation, however, it is suggested that each stenosis which was found "subcritical" in this study was higher than 80 %.

The most striking effect in response to hemodilution is the increase in cardiac output (CO). In the present study a 67 % increase in CO was

found, when hematocrit was lowered from 45 % to 15 %. *Fowler* and *Holmes* (8) described nearly doubled CO-values in response to anemia (Hct 44.4 % → 18.1 %). Similar results were found by *Escobar* et al. (7), *Glick* et al. (11), *Messmer* et al. (16), *Carey* et al. (4), *Murray* and *Rapaport* (18) and could be demonstrated in our control experiments. The difference between these values and the data given in the present paper is explained by the different experimental conditions. In contrast to our study where coronary perfusion to a relatively large area of the left ventricle was limited, the data given in the literature were found in hearts with intact coronary circulation.

Calculated total peripheral resistance decreased with progressive anemia due to the improvement of blood fluidity and the increase in total vascular cross section. This result is in accordance with the findings of other authors (17, 19, 24). The increase in the total cross sectional area of the vascular bed might be explained on a metabolical basis or by the improvement of blood fluidity per se (24, 8). The studies of *Murray* and *Escobar* (19) lend support to the concept that the decrease in blood viscosity is the responsible mechanism for the decrease in total peripheral resistance. The reduction of oxygen content at constant viscosity did not increase cardiac output. With dextran exchange anemia, however, cardiac output rose.

The reduction in afterload is suggested to be the primary cause for the increase in cardiac output (7, 8, 16). Besides this effect of hemodilution based on the improvement of blood fluidity additional mechanisms seem to be involved. *Escobar* and co-workers (7) concluded from their studies that improved cardiac performance in anemia is the result of both enhanced myocardial contractility and reduced afterload.

Murray and *Rapaport* (18) described an increase in myocardial contractility which in their opinion is caused by release of noradrenalin from sympathetic nerve endings or stores in the heart. In an earlier communication *Fowler* and *Holmes* (9) suggested that besides the reduction in afterload an unidentified humoral substance explains the improved or maintained left ventricular performance during anemia. *Messmer* and co-workers (15) did find no impairment of myocardial contractility with dextran exchange anemia using (dP/dt): IP as a contractile index. In previous studies in the isolated isovolumically beating dog heart no change in contractility during limited hemodilution could be demonstrated (13).

In the present paper (dP/dt): IP increased with progressive hemodilution, but the changes were not significant. The different experimental condition, however, does not allow a direct comparison with results obtained from hearts with intact coronary circulation. Another mechanism by which the heart could enhance its output is based on the *Frank Starling* law. *Rodriguez* and co-workers (26) found an increased enddiastolic volume with dextran exchange anemia. *Escobar* and associates (7) demonstrated a slight but insignificant increase of enddiastolic volume. From the elevation in left enddiastolic pressure at fairly constant enddiastolic volume they suggested decreased myocardial distensibility. Using enddiastolic segment length as a measure of initial fiber length

and enddiastolic volume our data from the control group – where hemodilution was performed in hearts with intact coronary circulation (compare fig. 6a) – demonstrate no significant increase with progressive anemia. LVedP, however, increased markedly. The pressure-length relationship (compare fig. 10a) shows a pronounced decrease in myocardial compliance. These findings confirm the results of previous studies in the isolated isovolumically beating heart (13). In our opinion, the decrease in myocardial distensibility is brought about by the excessive increase in coronary flow due to improvement of blood fluidity and reactive coronary vasodilation. Coronary volume capacity is widely filled up by the increased coronary flow enhancing total intracoronary blood volume and thus ventricular mural volume. The intravascular distension forces, which are transmitted more directly and less damped, and the rise in ventricular mass leads to an increase in initial fiber length. At a constant or even slightly increased left ventricular enddiastolic volume the LVedP rises. The enhanced intracoronary volume may be considered as an "additional preload". Left atrial pressure and pulmonary artery pressure increased demonstrating the compensatory effort.

The decrease in enddiastolic length at a constant contractile state is considered to be the result of both reduced afterload and increased preload. Despite the increase in LVedP at a constant left ventricular volume, *Escobar* and co-workers (7) suggested that an increase in initial fiber length cannot be implicated as the mechanism which the heart uses to enhance its output in acute experimental anemia.

Acute isovolumic dextran anemia leads to a preferential increase of coronary flow (18, 23, 30). Lowering hematocrit from 47.8 % to 19.3 %, *Murray* and *Rapaport* (18) found a 192 % increase in coronary flow. *v. Restorff* and associates (25) described a sevenfold increase of coronary flow in response to anemia (Hct → 12.5 %) in conscious dogs at rest. An excessive increase in coronary blood flow by diminishing hematocrit was also reported by *Bassenge* and co-workers (1) and *Case* et al. (5). In the present study a 211 % increase in blood flow in the intact LCA was noted when the hematocrit was lowered to 15 %. In contrast, the flow in the mechanically restricted LAD rose only by 47 % within the same hematocrit range. It is suggested that this small increase is caused by the decrease in blood viscosity at an already highly limited respectively depleted coronary reserve capacity. Myocardial function in the are supplied by the restricted LAD was progressively depressed. EDL increased continuously while ΔL fell. At a hematocrit level of 35 % ΔL was already reduced to 81 % and at 15 % hematocrit to 54 % of the initial value (compare table 1). This decrease in performance indicates insufficient coronary perfusion. Starting from a hematocrit of about 30 % local rhythmic disturbances as alternating contraction (compare fig. 9) were frequently observed besides hypokinesia. Below 22 % hematocrit signs of regional dysfunction at different severity as seen in states of myocardial ischemia (12) occurred (compare fig. 8 and 9). The velocity of shortening was progressively reduced until systolic bulging was fully developed.

The improvement of regional myocardial function in the area depending on the intact LCA must be considered as an attempt of the intact

myocardium to compensate for the hypokinesia in a relatively large part of the left ventricle. The restoration of myocardial function to normal and the disappearance of arrhythmia and ischemic signs in response to removal of the stenosis (compare fig. 8 and 9) demonstrates the reversibility of myocardial damage and the sufficient oxygen supply at this hematocrit level of 15 %, provided the coronary circulation is intact. These results are in agreement with the findings of *Case* et al. (5) who found that in the presence of coronary stenosis anemia accentuates the depression of ventricular function. *v. Restorff* and co-workers (25) also discussed the possible range of hemodilution in coronary vascular disease. In hearts with intact coronary circulation, *Buckberg* and *Brazier* (2) demonstrated that even with moderate hemodilution subendocardial ischemia can occur when oxygen requirements are raised by experimental aortic stenosis. The clinical success achieved with the use of hemodilution in patients with severe coronary artery disease reported by *Yoshikawa* et al. (32) is in contradiction to our results. No data, however, are available which demonstrate the improved perfusion or mechanical performance of the ischemic myocardium in response to hemodilution.

In other types of experiments the effect of hemodilution on the severity of myocardial ischemia during coronary occlusion was evaluated. The findings of *Nahas* et al. (21), *Ruiz* et al. (27), and *Yoshikawa* et al. (32) suggest that the severity of ischemia is decreased in response to hemodilution. These results, however – covering a special situation – may be misleading in the approach to detect the safe limits of hemodilution. After removal of the stenosis hemodilution could be continued until 8 % hematocrit was reached without any evidence for impairment of total or regional myocardial function. Temporary coronary occlusion, however, which was performed at different hematocrit levels demonstrated the marginal metabolic state at 10 % hematocrit as indicated by the increased recovery time (compare fig. 11).

Conclusion

The improvement of blood fluidity fails to cover the oxygen demands of the myocardium during progressive isovolumic anemia in a state of depleted coronary reserve capacity.

Reversion of hypokinesia after removal of stenosis shows that myocardial function is not impaired at a hematocrit as low as 15 %, provided the coronary circulation is intact.

Zusammenfassung

Während Hämodilution nimmt die Blutviskosität ab, und die aortale Eingangsimpedanz sinkt. Die klinische Anwendung bei Linksherzversagen wurde vorgeschlagen, jedoch sind die zu steckenden Grenzen der isovolämischen Hämodilution weitgehend unbekannt. In dieser Arbeit wurde untersucht, inwieweit die reduzierte O_2-Transportkapazität des Blutes unter normaler und eingeschränkter Koronarreserve die Funktion des linken Ventrikels beeinflußt.

Im akuten Experiment an 20 Hunden wurde die LAD subkritisch stenosiert und sowohl die Pumpfunktion des linken Ventrikels als auch die Koronarversorgung untersucht. Die regionale Myokardfunktion wurde nach dem Ultraschall-Laufzeitprinzip bestimmt. Dazu wurden piezoelektrische Wandler in die Wand des linken Ventrikels implantiert. Eine schrittweise Senkung des Hämato-

krit bis auf 15 % erfolgte durch isovolumischen Blutaustausch mit Dextran 60. Als Folge konnte ein Anstieg des CVP (+ 18 %), des PAP (+ 47 %), des LAP (+ 64 %), des LVedP (+ 46 %) und des CO (+ 67 %) verzeichnet werden. Der Blutfluß in die normal versorgten Myokardbezirke stieg um das dreifache (Q_{LCA}: + 211 %), während in der LAD nur eine geringfügige Flußzunahme registriert wurde. Die enddiastolische Länge EDL in den minderversorgten Myokardbezirken erhöhte sich auf 120 %; deren Kontraktionsamplitude ΔL fiel jedoch um 46 % ab. Zugleich wurde in den nichtischämischen Myokardarealen ein kompensatorischer Anstieg der ΔL um + 38 % bei nur minimal vergrößerter EDL (+ 9 %) deutlich. Nach Entfernung der Stenose kehrten die EDL und ΔL auf ihren Ausgangswert zurück.

Bei zunehmender Anämie kann der Sauerstoffbedarf in Myokardbezirken mit erschöpfter Koronarreserve nicht mehr in ausreichendem Maße gedeckt werden. In diesen Bereichen entsteht eine ischämische Dysfunktion. Die Gesamtventrikelfunktion kann jedoch durch kompensatorische Hyperkinesie des Restventrikels erhalten bleiben. Selbst bei einem Hämatokrit von 15 % ist die Hypokinesie nach Eröffnung der Stenose in den bislang ischämischen Arealen reversibel.

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