THE INVASIVE AND NON-INVASIVE EXAMINATION OF CIRCULATORY SYSTEM FOCUSED ON CHANGES IN DYNAMICALLY PERFUSED CORONARY CAPILLARY SYSTEM

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I. Introduction

The human body works like a system that contains many subsystems, all of them acting and counteracting to each other. To better understand them, one should measure at a specific time point or in case of more complex situation, the cycles of the living system. One of the most interesting and complex part of the human body is the circulatory system that can be observed by simple methods, such as palpate the pulse, or in a more sophisticated way, such as magnetic resonance (MR) measurements. One of the most important aspects of the system is to describe the normal function or to analyze the reaction to stress situation. Circulatory system can be well described with three independent parameters; such as pressure (P), volume (V) and time (t). During the daily practice we call them blood pressure (RR, wich is equal to P), heart rate (HR, wich is the reciprocal rate of time - heart beat over the one minute period). In critical condition we would like to measure the cardic output (CO) or cardiac index (CI) (CO equal flow, practically V/t). Many of our examination tools are not able to measure these three independent parameters at the same time by a noninvasive way, some times even very difficult to measure the correct data by invasively also. The control of the human body is very sophisticated and one of the key element of the circulatory system regulation is the endothelial cells. Vascular endothelium participates in various important physiologic processes, such as hormone synthesis and degradation, prostaglandin synthesis, release and uptake, lipid processing and xenobiotic metabolism. These functions of the different organs may be changed even when morphological or clinical signs of endothelial dysfunction are absent. Healthy human vascular endothel metabolize circulating substances and exhibit evidence of altered endothelial function during various conditions, including cardiopulmonary bypass and pulmonary hypertension, permeability edema, ARDS, etc.. Endothelial ACE function has been reported that various types of injury (bleomycin, hyperoxia, chest irradiation, phorbol ester acetate, cardiolplegic solution, etc.,) can affect the interaction of these enzymes with their substrates. Endothelial

cell injury also occurs in a number of chronic illnesses, notably autoimmune diseases, atherosclerosis and diabetes. The vascular pathology of diabetes mellitus has long been categorized into macroangiopathy and microangiopathy. Diabetic macroangiopathy is very similar to non-diabetic atherosclerotic lesions. The lesions, however, are more diffuse, more severe and more prominent in peripheral arteries.The pathogenesis of vascular disease is multifactorial, endothelial functional and structural injury however, appear to be an early event. Endothelial structural alterations, and adhesion of leukocytes and platelets onto the cell surface were apparent in diabetic rabbit aortas, as early as two weeks after alloxan injection. Impaired endothelium-dependent relaxation has been demonstrated in several species and vessel types.

Endothelium-bound ACE is an ideal probe for estimating the function and/or size of the perfused capillary bed, *in vivo,* a) because ACE is uniformly distributed throughout the luminal endothelial plasma membrane surface, including calveolae, b) because endothelium-bound ACE is an ectoenzyme, and this allows the repeated use of exogenously administered circulating substrates with negligible tissue accumulation of substrate or product, c) by virtue of the continuously increasing ratio of luminal wall surface area to luminal volume, as vessel diameter decreases, the highest hydrolytic activity is concentrated in capillaries, with less than 10% of total activity being attributed to vessels of diameter >20μm.

In the coronary microcirculation of the *in situ* beating heart, the variables of the *ex vivo* enzyme reactions (temperature, pH, buffer and ionic strength) are controlled by normal homeostatic mechanisms, however other parameters unique to the *in vivo* enzyme reaction (length and diameter of capillaries, spatial and temporal heterogeneity of blood flow, vasomotor control of capillary transit time and perfused endothelial surface area) and it could be widely variable depend on the physiological and/or pathophysiological changes .

The concepts of (coronary) microvascular recruitment and decruitment are based on the theory of coronary vascular reserve, the major element of coronary autoregulation. Since coronary blood flow depends on myocardial oxygen demand, myocardial capillary perfusion is spatially and temporally heterogeneous because the myocardial oxygen demand is heterogeneous. The heterogeneity of perfusion is based upon the flow patterns

of the coronary microcirculation which is composed of parallel capillaries joined at random intervals by anastomoses. This heterogeneity of coronary blood flow has been documented in several species, utilizing radiolabeled microspheres and multiple indicator dilution techniques. Multiple indicator dilution experiments have shown that the capillary permeability-surface (PS) product of select solutes changes in proportion to coronary flow changes although permeability changes and molecular size have effects on these measurements. Analysis of the effects of a wide range of flows on the coronary PS product demonstrated that the PS product is proportional to flow till maximal capillary recruitment, then remains constant at higher flows. The effects of coronary flow reduction on the PS product were studied by Harris et al. (1) using an opened chest canine model where flow was adjusted via clamping of a carotid-LAD cannula. Their results suggested that decreased coronary flow reduces surface area by capillary de-recruitment.

Millions of coronary angiographies, more than one million percutaneous transluminal coronary angioplasties and comparable number of coronary arterial bypass graft procedures are performed annually all over the world. The interpretation of coronary angiograms has shown significant intra- and inter-observer differences. Similarly, arteriograms of the stenotic segments do not give significant information about changes in the size of the perfused capillary surface area. *In vivo* estimation of endothelial-bound ACE activity as a new method, when combined with traditional coronary reserve measurement maneuvers (pacing, adenosine, papaverine, dipyridamole test, etc.) or when used during coronary artery bypass graft, percutaneous transluminal coronary angioplasty or left heart catheterization procedures, could provide a useful, objective tool for investigating alterations in the size of the perfused coronary capillary surface area in man.

Magnetic resonance imaging (MRI) could help to detect ischemic events in the heart and help to recognise the area under the risk during rest and stress conditions.

To prevent the possible loss or demage of myocardium would be the main target of the so - called preventive medicine. To test or analyse the reaction of circulatory system by non-invasively would be the powerful tool to decraese the morbidity and the mortality rate of the ischamic heart disease (IHD).

From bench to bedside, I tried to collect some of the examination tools to solve the above

mentioned problems such as in the animal experiment session 1. coronary reactivity measurement, 2. capillary surface measurement of the heart, 3. myocardial ischemic events detection in canine model. During the human studies healthy volunteers, to analyze the stability and reproducibility of the impedance cardiography and using the cold pressor test combined with the PRIMA (statistical pattern recognition method) to separate different type of subjects, were investigated. An other group of patients (underwent routine coronary angiography) were measured to validate the newly developed noninvasive device, so-called arteriograph.

II. Animal experiments

1. AgII and ET-1 interaction in dog model

(published as:

B. Kiss P, **Horváth I**, Szokodi I, Tóth P, Kékesi V, Juhász-Nagy A, Tóth M

Endothelin does not interact with angiotensin II in the coronary vascular bed of anesthetized dogs

J Cardiovasc Pharmacol 31[Suppl. 1]: S103-S105 (1998)

IF: 1.690)

Experimental protocol

To analyze the interaction of the two most aggressive vasoconstrictor agents such as AgII (angiotensine II) and ET-1 (endothelin-1), the following experiment was carried out:

Sixteen mongrel dogs of either sex weighing 10-23 kg were anesthetized by i.v. injection of pentobarbital sodium (30-35 mg/kg). Artificial positive pressure ventilation was started through an endotracheal tube by room air. Thoracotomy was performed between the fourth and fifth ribs and the heart was suspended in a pericardial cradle. An electromagnetic flow probe (Statham SP 2201) was placed around the LAD to measure blood flow and a small indwelling catheter (o.d. < 0.8 mm) was inserted into the LAD for administration of drugs. Unipolar electrodes were sewn onto the epicardial surface of both ventricles and atria for electrical stimulation and recording of electrocardiograms. Standard bipolar and unipolar surface ECG leads were continuously recorded. All parameters were recorded on a 12-channel direct writing recorder (Schwartzer). Before the experiments the animals were heparinized (500 mg/kg, i.v.).

Results (see figure 1.)

Bolus injections of AgII (7.8×10^{-13} to 3.9×10^{-11} M) and ET-1 (10^{-12} to 10^{-9} M) induced a dose-dependent decrease in coronary blood flow (CBF) ([DELTA]CBF_{max} -82± 10% for AgII and -91 ± 8% for ET-1). Simultaneous AgII and ET-1 boluses had slightly smaller effects on CBF than the calculated additive figure. Five-minute infusions of AgII (10^{-12} to

10^{-10} M/min) and ET-1 (5×10^{-12} to 2×10^{-10} M/min) induced a slight decrease in CBF ([DELTA]CBF_{max} -12± 9% for AgII and -19 ± 9% for ET). Background ET-1 or AgII infusions did not alter the dose-response curve of the other drug. Simultaneous Ag II and ET-1 infusions at different rates (10^{-12} to 10^{-10} M/min for AgII and 5×10^{-12} to 2×10^{-10} M/min for ET-1) over 5 min had similar effects on CBF as the calculated additive figure ([DELTA]CBF_{max} -35 ± 17% for the joint administration of the highest doses). Bolus administration of ET-1 and AgII resulted in transient coronary vasoconstriction. Similar amounts given over a 5-min period had only slight effects on coronary vascular tone. Bolus injections of the two drugs in combination resulted in a less degree of vasoconstriction than the calculated additive value from individual injections. Subthreshold background infusions of one drug did not influence the dose-response curve of the other drug. Joint infusions of the drugs in some cases resulted in greater effects than the calculated additive value from individual experiments.

Discussion

This study shows that AgII and ET-1 do not interact in the coronary vascular bed of anesthetized open-chest dogs when administered into the coronary artery. We postulate that joint administration of these two vasoconstrictor substances into the coronary artery can induce transient fulminant vasoconstriction reminiscent of unexplained fatal events of myocardial ischemia. In our experimental setting, drugs were administered into the LAD. Acting from the inside of the coronary vessels is only one way in which ET-1 (2,3) and AgII can influence coronary vascular tone. Circulating substances can also act from the endocardial side of the heart and, in fact, the endocardial control of heart function has been characterized in recent years. More importantly, AgII and ET-1 are produced locally in the heart. Paracrine effects of the drugs are probably more important and are poorly reflected in plasma levels. Finally, high levels of vasoactive substances were recently found in the pericardial fluid of dogs and cardiac patients (4), indicating that there are at least four functionally active compartments: the lumen of the coronary vessels, the heart chambers, the interstitial space, and the pericardial space. One interesting feature was that joint infusion of the two drugs decreased coronary vascular tone in some experiments more than

the calculated additive value of separate experiments. However, this was observed only in a small number of cases, and we were unable to characterize this subgroup of animals in any way that might explain the disproportional effect of the drugs. A similar phenomenon was not observed in any other setting, i.e., joint boluses or individual boluses superimposed on infusions of subthreshold doses of the other drug. Our findings do not exclude the possibility that ET-1 and Ang II can induce fatal vasoconstriction, but rather indicate that subthreshold intracoronary doses are insufficient to induce such an effect.

2. Perfused coronary surface measurements in dog

(published as:

B. Horvath IG, Cziraki A, Parkerson JB, Khan SU, Catravas JD
Effect of acute coronary occlusion on the size of the dynamically perfused coronary capillary bed in the dog
Microvasc Res 56: 95-100 (1998)
IF: 1.425)

Experimental protocol

Experiments were performed using seven mongrel dogs (five males and two females), weighing 18.6–28.6 kg (mean 22.2 ± 0.8 kg). All animals were anesthetized with sodium pentobarbital, 30 mg/kg i.v., and artificially ventilated. Polyethylene cannulas were inserted into a femoral vein for drug administration, a femoral artery was cannulated for continuous monitoring and recording of systemic blood pressure, and electrocardiogram was recorded from standard limb leads (I or II) (Gould 2400; Gould Instruments, Columbus, OH). After a transverse chest incision, the pericardium was opened, the beating heart was isolated by pericardial cradle, and the following procedures were performed: (1) pediatric angiographic balloon catheters (4F Arrow Int., Inc., Reading, PA) were inserted into the left and right atria; (2) two segments of the left anterior descendent artery (LAD) were dissected from the underlying myocardium; (3) a mechanical occluder (surgical suture) and electromagnetic flow probe were placed around the proximal segment of the LAD; the flow probe was

connected to a flow meter (CliniflowII, Carolinas Medical Electronics, King, NC); and (4) the distal segment of the LAD was cannulated with a polyethylene cannulas (o.d. 0.8 mm) for isotope injections. After surgical preparation, heparin 300 U/kg (Elkin-Sinn, Inc., Cherry Hill, NJ) was administered intravenously. Animal handling and euthanasia were in accordance with guidelines approved by the Institutional Committee on Animal Use for Research and Education (Medical College of Georgia, Augusta, GA).

After the surgical procedure was completed, eight measurements were performed, at approximately 15-min intervals. Two transpulmonary measurements of ACE activity and perfused capillary surface area were carried out before (P1) and after (P2) the six transcoronary measurements. Three transcoronary measurements were performed, at 50% flow reduction (E1), at 75% flow reduction (E2), and after ligation (E3) of the first diagonal branch (distal to the flow probe) of the LAD. Each measurement took place 5 min after reduction of flow; coronary flow was returned to normal immediately after the E1 and E2 measurements. Control (C1, C2, and C3) transcoronary measurements were carried out before each LAD flow reduction and served as baseline values for E1, E2, and E3 measurements, respectively. LAD flow reductions (E1, E2) were achieved by partially occluding the previously placed mechanical occluder.

Transpulmonary Measurements: For each transpulmonary measurement, 2 μCi of the synthetic ACE substrate [3H]benzoyl-Phe-Ala-Pro ([3H]BPAP) was injected into the right atrium and blood was withdrawn immediately from the left atrial catheter at a rate of 0.71 ml/s, by means of a roller pump, into a fraction collector equipped with 13x100-mm borosilicate tubes, advancing at the rate of 1 tube/0.7 s (0.5 ml/tube). We have previously shown that both substrate and product remain within the vascular spaces during a single transpulmonary passage.

Transcoronary Measurements: Before coronary measurements were performed, the tip of the right atrial cannula was repositioned into the coronary sinus and the position was verified manually. For each coronary measurement, 2 μCi [3H]BPAP was injected into the LAD cannula and simultaneously, blood was withdrawn from the coronary sinus catheter at the rate of 0.17 ml/s by means of a roller pump into a similarly equipped fraction collector (0.12 ml/tube). In preliminary experiments, the intravascular indicator indo-cyanine green

was co-injected with [3H]BPAP; the outflow curves thus obtained were congruent, indicating that in the coronary, as in the pulmonary circulation, substrate and product remain within the vascular spaces during a single transcoronary passage.

Determination of [3H]BPAP Hydrolysis by Coronary or Pulmonary Capillary Endothelium-Bound ACE: Each sample tube in the fraction collector contained 2 ml of 3 mM 8-hydroxyquinoline-5-sulfonic acid and 1 mM EDTA in normal saline to prevent any further metabolism of BPAP by serum ACE. The sample tubes were centrifuged at 3000 rpm for 10 min to separate cells from plasma. Two 0.5-ml aliquots of the supernatant from each tube were transferred into each of two 7-ml polyethylene scintillation vials (Fisher Scientific, Atlanta, GA). Total 3H activity (total 3H) was measured in one set of vials in the presence of 5 ml of Ecoscint A scintillation cocktail (National Diagnostics, Atlanta, GA) by a liquid scintillation spectrometer (Model LS 7500; Beckman Instruments, Irvine, CA). The second 0.5-ml aliquot was mixed by inversion with 2.5 ml of 0.12 N hydrochloric acid and radioactivity was estimated in the presence of 3 ml of 4 g/liter Omnifluor (Dupont, Boston, MA) in toluene (Baxter, Muskegon, MI), after 48 h of undisturbed equilibration in the dark. In this manner, 61% of the metabolite ([3H]benzoyl-Phe; P) and ~5% of the unmetabolized substrate ([3H]BPAP; S) are extracted into the toluene (counting) phase, the precise fraction determined as previously described below. Substrate utilization was estimated as

$$\nu = \ln[(S+P)/S]$$

integrated over the entire transpulmonary or transcoronary passage.

Calculation of the Size of the Dynamically Perfused Capillary Surface Area: Amax/Km (proportional to the size of the dynamically perfused capillary surface area) was calculated from linear regression of the integrated form of the Henri–Michaelis–Menten equation, under first-order reaction conditions,

$$A_{max}/K_m = E * k_{cat} / K_m = (Q_p / (\alpha / t_{mean} * t + 1 - \alpha))* \nu$$

where Q_p is plasma flow; A_{max} is the product of enzyme mass, E, and k_{cat}, the catalytic rate constant; K_m is the Michaelis constant; t_{mean} is mean transpulmonary or transcoronary 3H transit time; and t is sample collection time [4]. Thus, changes in the size of the dynamically perfused capillary surface area are reflected in changes of enzyme mass, i.e.,

changes in the quantity A_{max} /K_m. The parameter a is a dimensionless perfusion parameter related to the relative amount of total bolus dispersion. When capillary transit times are nearly homogeneous, approaches zero (i.e., the capillary bed is homogeneously perfused), and as capillary perfusion heterogeneity increases, the a value becomes larger [22]. Plasma flow was computed as the product of blood flow (estimated from the electromagnetic flow probe) and 1-hematocrit.

Mean transit time (t mean) was calculated as:

t_{mean} (S) = t [3 H] dt / [3 H] dt

Mean transit time was corrected for the catheter transit time. In the above equation, t_{mean} represents mean transit time from the right atrium to the left atrium during P1 and P2 or from the flow-controlled LAD to the coronary sinus during C1–3 and E1–3 measurements; t is sample collection time [30].

Statistical analysis

Data are presented as means ± SEM. Statistical calculations were performed using appropriate statistical software (Statpak, Northwest Analytical, Portland, OR). Statistical comparisons utilized Student's t test for paired samples or one-way ANOVA for repeated measures as appropriate. Differences were considered significant at $P < 0.05$.

Results

Hematocrit (47 ± 1.3%), arterial pH (7.39 ± 0.01), pCO2 (37 ± 1 mm Hg), and pO2 (99 ± 2 mm Hg) values remained within physiologically normal ranges throughout each experiment. There were no significant changes in mean arterial blood pressure, heart rate, mean transit time, or a values between the two pulmonary and between each of the three pairs of coronary measurements (Table 1).

Similarly, there were no significant differences in mean arterial pressure or heart rate values during the entire course of the study and no differences in mean transit time or a values among any of the coronary determinations. Typical transpulmonary and transcoronary effluent plasma isotope curves from one experiment are shown in Fig. 2.

Fractional concentrations of tritium (FC, sample dpm/total dpm injected) in the effluent plasma, single-pass substrate utilization (v) of [3H]BPAP are plotted for the pulmonary

and the coronary vascular beds. Within each determination, individual sample values of v did not vary significantly during the transpulmonary measurements but presented a time-dependent increase during transcoronary measurements, probably reflecting differences in the degree of capillary perfusion heterogeneity between the two organs. Reproducibility of v values among successive determinations was quite good: among all control transcoronary measurements, variance was calculated at 0.03 (4.7%). No significant changes in pulmonary blood flow (1799 ± 168 ml/min vs 1391 ± 168 ml/min), transpulmonary substrate utilization (1.53 ± 0.11 vs 1.58 ± 0.06) or Amax/Km (1526 ± 206 ml/min vs 1237 ± 179 ml/min) were observed between the first (P1) and the last (P2) transpulmonary measurements, suggesting a stable preparation. Similarly there were no significant changes in coronary blood flow, v, and Amax/Km among the three control, C, transcoronary measurements.

Figure 3. shows the results from the first pair of transcoronary measurements, i.e., before (C1) and after (E1) LAD flow was moderately reduced by approximately 50%. Regional coronary blood flow (RCBF) was reduced significantly from 18.0 ± 1.7 (C1) to 6.5±1.0 ml/min (E1) after partial occlusion of the LAD. As a result, the parameter Amax/Km decreased from 6.6 ± 0.7 (C1) to 2.5 ±0.4 (E1) ml/min. On the other hand, substrate utilization (v) and percentage metabolism did not change significantly, 0.68 ± 0.01% (C1) vs 0.68 ± 0.04% (E1) and 49.3 ± 0.9% (C1) vs 49.2 ± 2.1% (E1). Comparable results were obtained after LAD flow was reduced by approximately 75% (Fig. 4.)

Consequently, Amax/Km decreased from 6.4 ± 0.9 (C2) to 1.1 ± 0.3 (E2) ml/min. No significant changes in substrate utilization (0.64 ±0.08 vs 0.66 ± 0.06) were observed. Utilizing a different approach to reduce RCBF, the first diagonal branch of the LAD was mechanically occluded. As shown in Fig. 5., a significant reduction in regional coronary blood flow was observed (from 21.6 ± 3.1 to 8.0 ± 1.3 ml/min) and consequently a significant decrease in Amax/Km (from 7.5±1.2 to 3.0±0.6 ml/min). [3H]BPAP utilization again remained unchanged during this procedure (0.60 ± 0.07 vs 0.61 ± 0.09).

When data from all the occlusion maneuvers were examined together, a significant linear correlation was observed ($y=0.36x+0.066$ $r=091$ $p<0.001$) between the measured regional coronary blood flow and the calculated Amax/Km (Fig. 6).

Discussion

Endothelium-bound ACE (5, 6, 7, 9) is an ideal probe for estimating the size of the perfused capillary bed, in vivo, (a) because ACE is uniformly distributed throughout the luminal endothelial plasma membrane surface, including caveolae (; (b) because endothelium-bound ACE is an ectoenzyme, and this allows the repeated use of exogenously administered circulating substrates with negligible tissue accumulation of substrate or product; because by virtue of the continuously increasing ratio of luminal wall surface area to luminal volume, as vessel diameter decreases, the highest hydrolytic activity is concentrated in capillaries, with less than 10% of total activity being attributed to vessels of diameter >20 mm. This is more readily seen in Fig. 7.

Furthermore, BPAP is an excellent substrate for ACE. It is pharmacologically inactive, exhibits high affinity for the enzyme, is restricted within the vascular spaces during a single transcoronary or transpulmonary passage, and is readily detected in plasma. In addition, because of the very low physiologic plasma concentration of angiotensin I and bradykinin relative to their Km for ACE, neither natural substrate competes with BPAP for hydrolysis. It should be noted that while there is uniform ACE distribution within capillaries, there may be heterogeneous distribution of capillaries across the cardiac wall which would necessarily be reflected in results with the present method. In the coronary microcirculation of the in situ beating heart, the variables of the ex vivo enzyme reactions (temperature, pH, buffer, and ionic strength) are controlled by normal homeostatic mechanisms, however other parameters unique to the in vivo enzyme reaction (length and diameter of capillaries, spatial and temporal heterogeneity of blood flow, vasomotor control of capillary transit time, and perfused endothelial surface area) change dynamically. The concepts of coronary recruitment and derecruitment are based on the theory of coronary vascular reserve, the major element of coronary autoregulation. Since coronary blood flow depends on myocardial oxygen demand, myocardial capillary perfusion is spatially and temporally heterogeneous because the myocardial oxygen demand is heterogeneous. The heterogeneity of perfusion is based upon the flow patterns of the coronary microcirculation which is composed of parallel capillaries joined at random intervals by anastomoses. This heterogeneity of coronary blood flow has been documented in several species, including the

dog, utilizing radiolabeled microspheres and multiple indicator dilution techniques. Multiple indicator dilution experiments have shown that the capillary permeability-surface product (PS) of select solutes changes in proportion to coronary flow changes (1), although permeability changes and molecular size have effects on these measurements. Analysis of the effects of a wide range of flows on the coronary PS product demonstrated that the PS product is proportional to flow till maximal capillary recruitment, then remains constant at higher flows. The effects of coronary flow reduction on the PS product were studied by Harris et al. using an opened chest canine model where flow was adjusted via clamping of a carotid-LAD cannula. Their results suggested that decreased coronary flow reduces surface area by capillary derecruitment. In the present study, the regional Amax/Km is analogous to the PS product. There were no significant differences in substrate utilization between two successive control determinations (at similar flow), indicating that capillary enzyme activity was unaltered during the experiment. Our data demonstrated a linear correlation between coronary flow and the size of the perfused capillary surface area (Amax/Km), without providing information about absolute changes in perfused coronary capillary surface or the source of regional flow heterogeneity. Myocardial perfusion can be measured by various methods. The optimal method would be noninvasive with high temporal and spatial resolution (8,10). unfortunately, this is not presently available. The method presented here has certain limitations: it is invasive, and endothelial injury may affect substrate (BPAP) utilization. However, it provides an accurate, reproducible, quantitative index of the relative size of myocardial perfusion (including the collateral circulation) and can be readily used in the clinic. On the other hand, the altered substrate utilization caused by hypoxia, reperfusion, or toxic agents could provide a marker to monitor the severity of endothelial injury. More than 1 million coronary angiographies, approximately 100,000 percutaneous transluminal coronary angioplasties, and a comparable number of coronaryarterial bypass graft procedures are performed annually in the United States. The interpretation of coronary angiograms has shown significant intra and interobserver differences. Similarly, arteriograms or the pressure gradient across one of the stenotic segments do not give significant information about changes in the size of the dynamically perfused capillary surface area. The present method, when combined with

traditional coronary reserve measurement maneuvers (pacing, adenosine, papaverine, dipyridamole, etc.) or when used during coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or left heart catheterization procedures, can provide a useful, objective tool for investigating alterations in the size of the perfused coronary capillary surface area in man.

3. Cardiac MRI for the diagnosis of ischemic events in the heart

(published as:

B. Simor T, Gaszner B, Oshinski JN, Waldrop SM, Pettigrew RI, **Horvath IG**, Hild G, Elgavish GA

Gd(ABE-DTTA)-enhanced cardiac MRI for the diagnosis of ischemic events in the heart

J Magn Reson Imaging 21: 536-45 (2005)

IF: 2.41)

Experimental protocol

ECG-gated, T1-weighted MR image sets (four to five slices each) with three-minute time resolution were collected in transiently LAD-occluded dogs. Following the acquisition of control image sets, ischemia was started by occluding the LAD. Either Gd(ABE-DTTA) (N = 6) or Gd(DTPA) (N = 6) was injected, and imaging was continued for 30 minutes of ischemia and 40 minutes of reperfusion. The contrast agent (CA)-induced MRI signal intensity enhancement (SIE) and contrast were monitored. Microspheres measured myocardial perfusion (MP) to verify areas of ischemia and reperfusion.

Results

SIEs of 86% ± 3% and 97% ± 3% in nonischemic, and 25% ± 5% and 29% ± 8% in ischemic regions were found within three minutes of onset of ischemia with Gd-(ABE-DTTA) and Gd(DTPA), respectively. For the rest of the 30 minutes of ischemia, with Gd(ABE-DTTA) SIE of 60% ± 3% and 25% ± 5% persisted in the nonischemic and ischemic regions, respectively. With Gd(DTPA), however, SIE in the nonischemic areas decreased rapidly after the first three minutes of ischemia, while SIE in the ischemic areas

increased, abolishing contrast. Thus, there was a persistent contrast with Gd(ABE-DTTA) and a short-lived contrast with Gd(DTPA) during ischemia. Furthermore, with Gd(ABE-DTTA) some contrast was still visible in the early reperfusion period. (see fig.8.,).

Discussion

Our study demonstrates that Gd(ABE-DTTA)-enhanced ceMRI (13-24), which shows persistent effects during ischemia and dissipation of contrast in a myocardial perfusion-dependent manner during reperfusion, enables the detection of ischemic events in the heart. The persistent effect of Gd(ABE-DTTA) allows direct measurements of R1 to be obtained, and thus quantification of myocardial perfusion becomes achievable. The ability of this agent to confirm the onset of reperfusion may be useful in determining the endpoint of an ischemic event and thus confirming the success of an interventional or medical treatment. Likewise, in the setting of a stress test, this agent could be used to confirm the demand-induced onset of ischemia. Thus our agent can be used analogously to a single-injection-thallium-201 test in clinical use to show both ischemia and reperfusion with a single bolus (11,12). Because of these characteristics, Gd-(ABE-DTTA) is potentially useful for several clinical applications. Such applications may include high resolution cardiac MRI for the quantitative detection of perfusion differences in stable angina, silent ischemia, and acute coronary syndrome, and determining areas of risk at rest and under stress conditions.

III. Human studies

1. Impedance cardiography (ICG) measurements

(published as:

B. **Horváth I**, Juricskay I, Mezey B, Vincze Á, Mózsik Gy

Effect of the cold pressor test in healthy and hyperacid subjects

J Physiology - Paris 87: 375-378 (1993)

IF: 1.095

C. **Horváth I**, Mezey B, Juricskay I, Simon A, Jávor T.:

Data for the evaluation of impedance cardiographic measurements

Card. Hung. 1:29-32 (1993)

Study design

The aims of the studies were to analyze the stability of ICG (25-37) (see fig. 9.,) and to estimate the effects of cold pressor test (CPT) on hemodynamic changes and to analyze the differences in the changes between normal and hyperacid subjects.

Methods:

12 healthy volunteers (negative anamnesis, ECG and normal hemodynamic state) were involved in study. Basic and calculated hemodynamic parameters (Z_0 – basic impedance, VET – ventricular ejection time, PEP – preejection period, SV- stroke volume, CO – cardiac output, CI – cardiac index, SVR – systemic vascular resistance) were recorded by ICG during resting (for stability, see fig.10.,) and they were recorded 4hour and 24hour later (for reproducibility, see table 2.,). We also compared the parameters recorded simultaneously by ICG and spiroergometry (see fig. 11.,).

Another 12 healthy volunteers (negative anamnesis, ECG and normal hemodynamic state) and 12 hyperacid patients (documented with pentagastrin test and similarly negative cardiovascular anamnesis, ECG and normal hemodynamic state) were involved in the discrimination study. Hemodynamic state of the subjects were recorded by ICG during resting – stability, stress (cold pressor test, right hand was immersed to ice water) and

during recovery phase (see 12., 13.). The relative changes were calculated and the data for the normal and hyperacid subjects were analyzed by unpaired t-test, finally PRIMA method as a multivariate statistical analysis was used.

Results

Based on the stability and reproducibility measurements, the Z_0 parameter is the best to analyze and/or compare data intraindividually . During the exercise period the correlation between ICG and spiroergometry was good (r = 0.81 fig. 11.). During the pentagastrin test, in a short time period a higher increase in HR (heart rate) was observed in normal subjects whereas the same time Z_0, RR_{sys}, RR_{dia}, VET were higher in hyperacid group (see fig. 12.,13.). As we expected after the learning phase of PRIMA could well separate the two different groups of volunteers (see fig. 14.,) .

Discussion

First we analyzed the stability and reproducibility of the ICG parameters. Based on the relative changes we conclude that the basic, measured parameters more stabile than the calculated parameters.

„Analyzing the effects of stress reaction is the most interesting problem of physiology and pathophysiology" (Greene at al 1965). Our newly developed CPT-ICG-PRIMA method could analyze the hemodynamic reaction of the human body by noninvasive way and could separate the different patients.

2. *Arteriograph validation study*

Study design

We validated a newly developed simple, user independent and fast oscillometric, portable device (Arteriograph) measuring augmentation index (Aix) and aortic pulse wave velocity (PWV-ao) simultaneously against invasive, intra-arterial measurements of the mentioned parameters (37,38). Our comparative study was performed on patients who underwent routine coronarography for diagnostic purposes. In 10 cases we measured the brachial Aix (Aix-br) with intra-brachial cannula and Arteriograph, and in 13 cases the aortic Aix (Aix-

ao) with intra-aortic catheter and the Aix-br with Arteriograph simultaneously on identical pulses. In 27 cases the invasively and non-invasively measured PWV-ao was compared. Out of the 27, in 11 cases we used 2 catheters (inserted from radial and femoral artery) positioned to the aortic root and to the aortic bifurcation and the transit time of the pulse wave was measured on identical heart cycles. In the remnant cases the PWV-ao was determined with one catheter with pull back from the aortic root to the bifurcation and the transit time was measured using ECG gating. All of the invasively measured transit time was determined by intersecting tangent algorithm on the pulse waves recorded in the aortic root and bifurcation. The aortic root-bifurcation distance was measured by marking the cannula in the aortic root and after its pull back to the bifurcation, and was compared to the non-invasively measured sternal notch-pubic bone distance.

Results (see fig. 15.,16.,17.)

The correlation between invasively and Arteriograph measured Aix-brachial/brachial, Aix-aortic/brachial and PWV-ao were 0,92 ($p<0,001$), 0,92 ($p<0,001$) and 0,82 ($p<0,001$) respectively. With Bland-Altman plots the differences were within 2SD in all of the compared parameters and no significant deviation from the zero line was found in different ranges of the measured values. The aortic root-bifurcation and sternal notch-pubic bone distance strongly correlated to each other ($R = 0,75$, $p<0,001$) and the difference (0,4 cm) between their means did not prove to be significant ($p=0,36$).

Conclusions

The new oscillometric Arteriograph device can measure accurately the central (aortic) and peripheral (brachial) Aix and aortic PWV. The simplicity (due to the oscillometric principle) of the use of this new method to determine stiffness parameters may help to spread more widely, even in primary care the measurement of the arterial stiffness parameters, of which importance is gaining ground rapidly nowadays in the detection of asymptomatic arterial disease.

IV. Summary and thesis

1. Using a canine model and based on the intracoronary administration of two vasoactive agents such as ET-1 and Ang II we conclude that they do not interact in the coronary vascular bed. One interesting feature was that joint infusion of the two drugs decreased coronary vascular tone in some experiments more than the calculated additive value of separate experiments. However, this was observed only in a small number of cases, and we were unable to characterize this subgroup of animals in any way that might explain the disproportional effect of the drugs. Our findings do not exclude the possibility that ET-1 and Ang II can induce fatal vasoconstriction, but rather indicate that subthreshold intracoronary doses are insufficient to induce such an effect.

2. Endothelium-bound ACE is an ideal probe for estimating the size of the perfused capillary bed, in vivo, (a) because ACE is uniformly distributed throughout the luminal endothelial plasma membrane surface, including caveolae (b) because endothelium-bound ACE is an ectoenzyme, and this allows the repeated use of exogenously administered circulating substrates with negligible tissue accumulation of substrate or product.

3. An earlier published results (Harris et al) suggested that decreased coronary flow reduces surface area by capillary derecruitment. In our study, the regional Amax/Km is analogous to the PS product. There were no significant differences in substrate utilization between two successive control determinations (at similar flow), indicating that capillary enzyme activity was unaltered during the experiment. Our data demonstrated a linear correlation between coronary flow and the size of the perfused capillary surface area (Amax/Km), without providing information about absolute changes in perfused coronary capillary surface or the source of regional flow heterogeneity.

4. Our MRI study demonstrates that Gd(ABE-DTTA)-enhanced ceMRI, which shows persistent effects during ischemia and dissipation of contrast in a myocardial perfusion-dependent manner during reperfusion, enables the detection of ischemic events in the heart. The persistent effect of Gd(ABE-DTTA) allows direct measurements of R1 to be obtained, and thus quantification of myocardial perfusion becomes achievable.

5. Based on the relative changes of the ICG data during the stability measurements we conclude that the basic, measured parameters more stabile than the calculated parameters.

6. Analyzing the results of the newly developed combined CPT-ICG-PRIMA method (which practically a statistically powered stress analysis) we could separate different group of patient based on the responder organs (analyzing of the heart reaction could separate the gastrointestinal vagal tone or reaction).

7. The new oscillometric Arteriograph device can measure accurately the central (aortic) and peripheral (brachial) Aix and aortic PWV, which means that by noninvasivaly could be measured the marker of rigidity of vascular system.

V. Publications

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1. Az értekezéshez kapcsolodó közlemények

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VII. Tables

Heart Rate (HR), Mean Arterial Pressure (MAP), Mean Transit Time (MTT), and α Values (Mean ± SEM)

	P_1	C_1	E_1	C_2	E_2	C_3	E_3	P_2
HR (b/min)	146 ± 8	145 ± 9	144 ± 9	137 ± 10	138 ± 10	138 ± 8	139 ± 8	145 ± 8
MAP (mm Hg)	93 ± 4	95 ± 4	94 ± 3	98 ± 6	97 ± 6	97 ± 5	93 ± 6	92 ± 3
MTT (s)	9.8 ± 2.0	8.1 ± 1.4	6.66 ± 1.1	7.20 ± 1.0	6.56 ± 0.82	7.60 ± 1.2	7.62 ± 1.1	9.7 ± 1.3
α	0.20 ± 0.04	0.60 ± 0.04	0.42 ± 0.11	0.7 ± 0.08	0.6 ± 0.18	0.50 ± 0.08	0.61 ± 0.09	0.22 ± 0.13

Note. There were no significant changes between each pair of pulmonary or coronary measurements.

Table 1. Baseline parameters of pulmonary and coronary the measurements.

	mean		SD	
	4h	24h	4h	24h
Zo	3,4	3,1	2,27	4,01
HR	9,4	8,9	6,46	5,33
PEP	6,5	7,2	5,50	7,92
VET	3,4	6,2	1,96	7,71
SV	7,3	7,6	9,77	9,58
CI	10,4	9,1	7,25	6,02
SVR	15,9	7,5	10,28	7,01

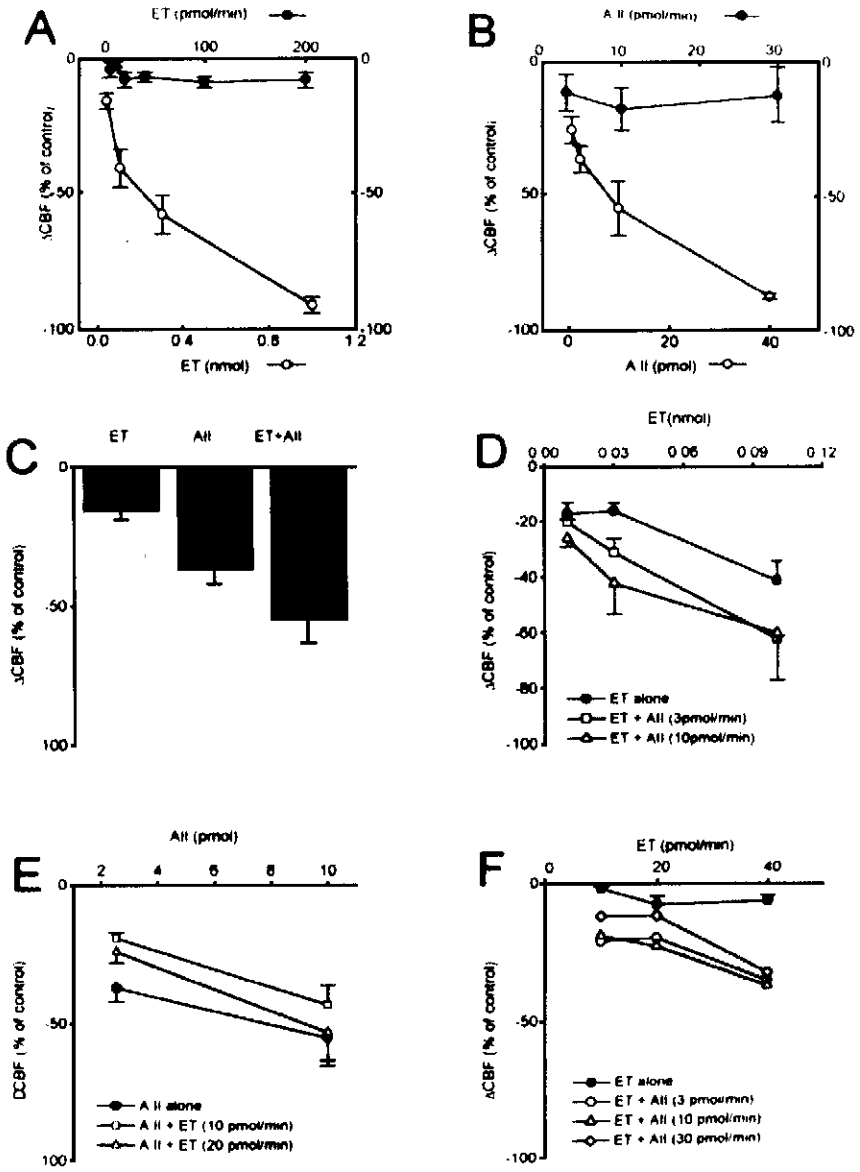
Expressed in %; n=10

Table 2.

Reproducibility measurements, 4h and 24h control compare to baseline. Relative changes expressed in %. Z_0 and VET are the best reproducible parameters.

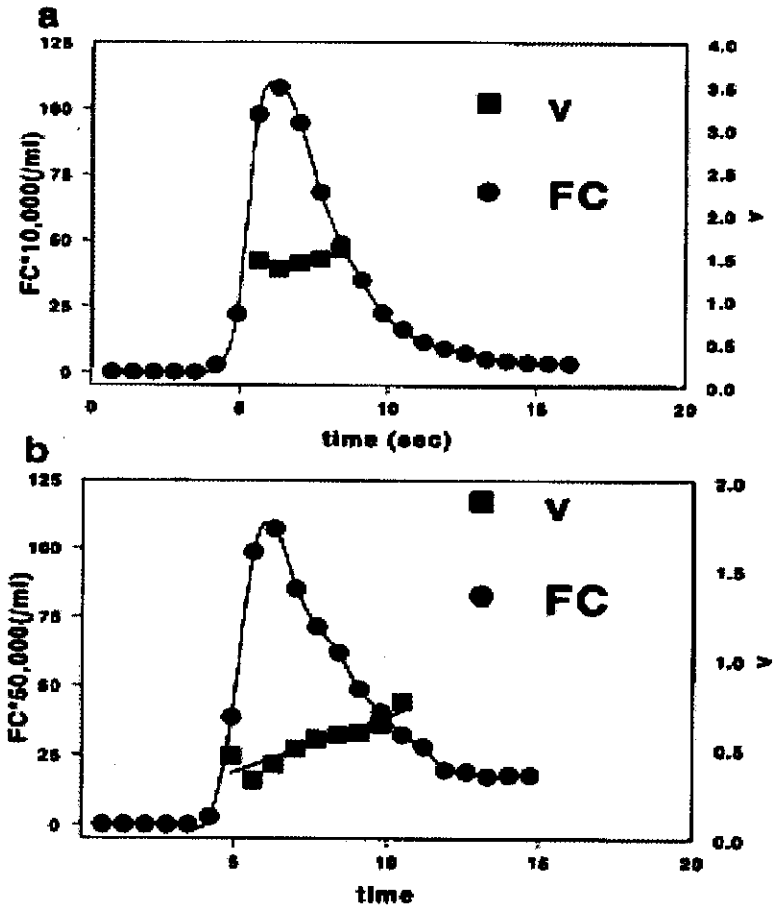
(z_0=basic impedance, HR=heart rate, PEP=pre-ejection period, VET=ventricular ejection time, SV=stroke volume, CI= cardiac index, SVR=systemic vascular resistance)

VIII. Figures



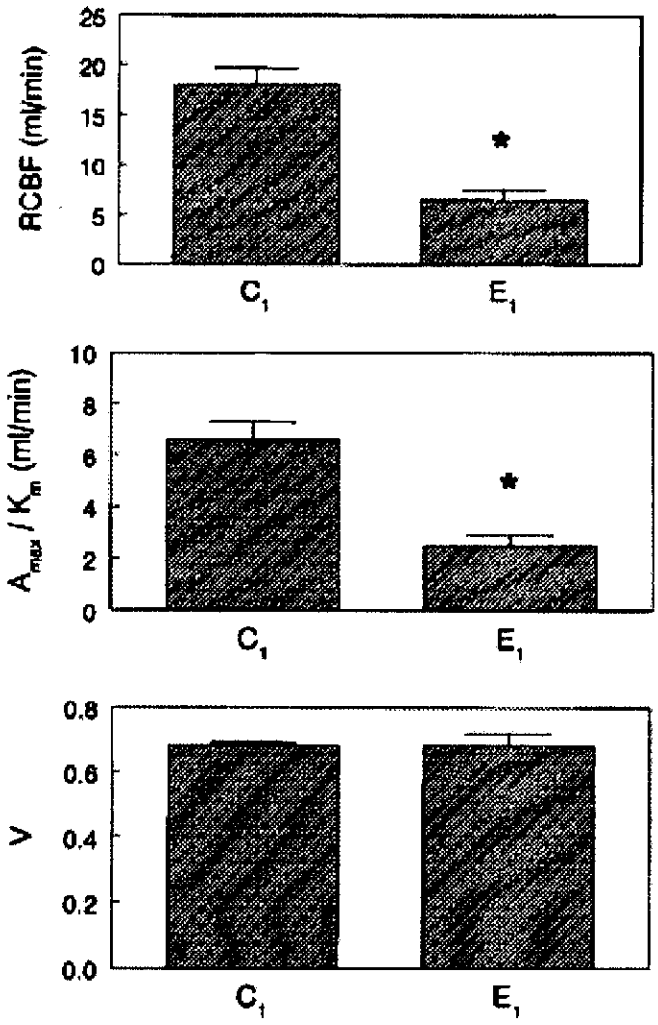
Effect of intracoronary administration of ET-1 and AgII (AII) on coronary blood flow in dogs. Drugs were administered into the left anterior descending coronary artery (LAD) via an indwelling catheter, either as boluses or as a 5-min infusions. The effect of each drug was also tested superimposed on background subthreshold infusions of the other drug. A: Effect of ET-1 boluses and infusions alone. B: Effect of AgII boluses and infusions alone. C: Joint effects of ET-1 and AgII boluses resulting in additive values. D: Effect of ET-1 boluses alone or with various background infusions of AgII. E: Effect of AgII boluses alone or with background ET-1 infusions. F: Effect of ET-1 infusions alone or with various AgII background infusions. Presented data are sown as mean±SEM. SEM bars are omitted from F panel because of wide variations.

Figure 1.



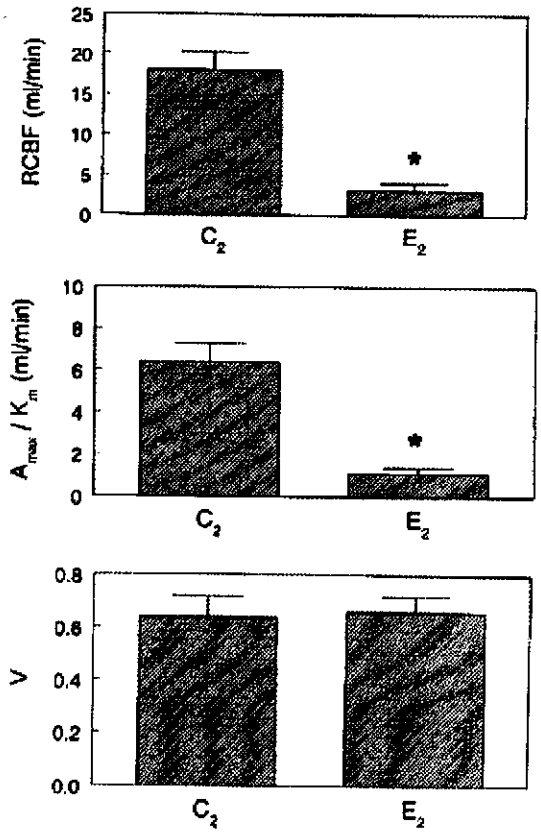
Indicator dilution curves of [^{3}H]benzoyl-Phe-Ala-Pro (BPAP) in the pulmonary (a) and in the coronary (b) vascular beds. Fractional concentration of total tritium in effluent plasma (FC) and substrate utilization (v) of [^{3}H]BPAP were calculated for each sample.

Figure 2.



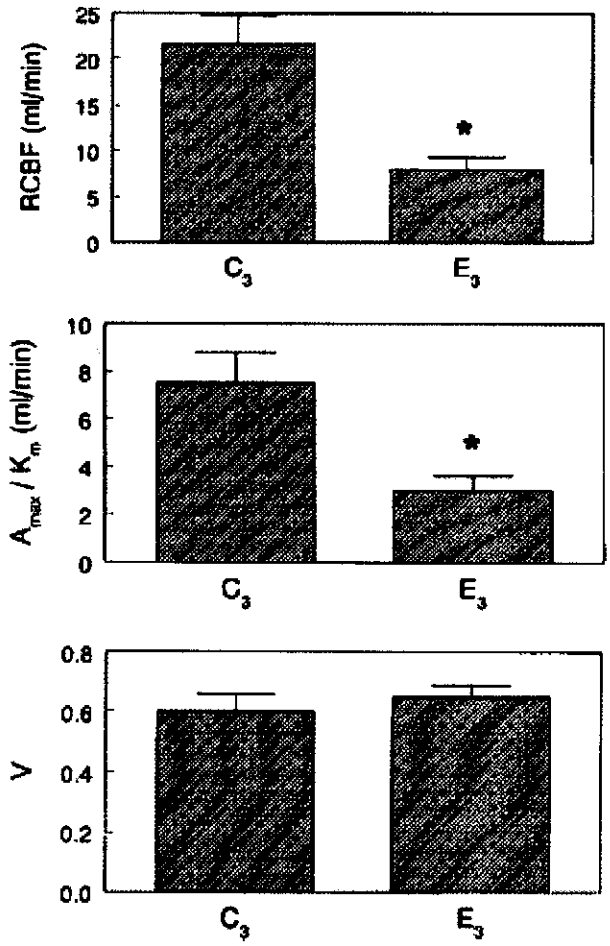
Changes in regional coronary blood flow (RCBF), substrate utilization (v), and A_{max}/K_m before and after LAD flow was moderately reduced to approximately 50%. C_1, control flow condition; E_1, reduced flow condition; means ± SEM; $^*P < 0.05$ from C_1.

Figure 3.



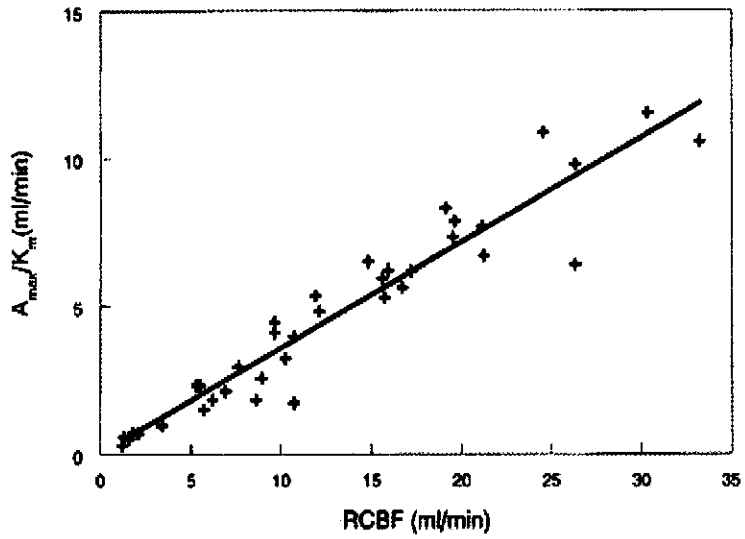
Changes in regional coronary blood flow (RCBF), substrate utilization (v), and A_{max}/K_m, before and after LAD flow was reduced by approximately 75%. C_2, control flow condition; E_2, reduced flow condition; means ± SEM; $^*P < 0.05$ from C_2.

Figure 4.



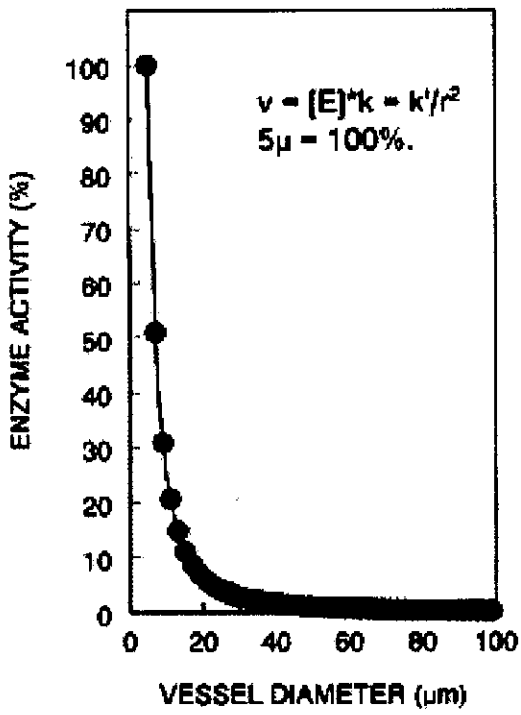
Changes in regional coronary blood flow (RCBF), substrate utilization (v), and A_{max}/K_m before and after regional blood flow was reduced by ligating the first diagonal branch of the LAD. C_3, control flow condition; E_3, reduced flow condition; means ± SEM; $^*P < 0.05$ from C_3.

Figure 5.



Correlation between regional coronary blood flow (RCBF) and size of the perfused coronary capillary surface area (A_{max}/K_m). Data combined from all maneuvers of reduced coronary flow ($N = 38$). $y = 0.36x + 0.066$; $r = 0.91$; $P < 0.001$.

Figure 6.



Correlation between vessel diameter and vessel wall enzyme activity assuming cylindrical vessels with 100% activity at a capillary of 5 μm diameter. As shown, more than 90% of enzyme activity (i.e., substrate hydrolysis) resides in vessels with diameter of 20 μm or less. $k = k_{cat}/K_m$, $k' = k \times E/(\pi \times l)$, where l is capillary segment unit length; E, enzyme mass of capillary of l length and r radius.

Figure 7.

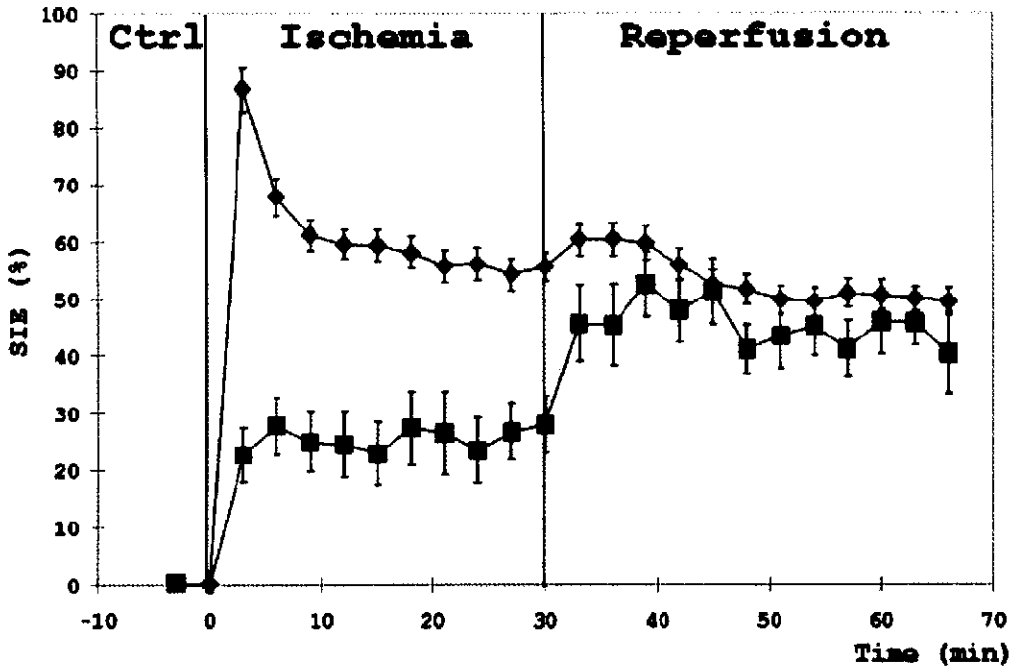


Figure 8a. see expl. Fig. 8c.

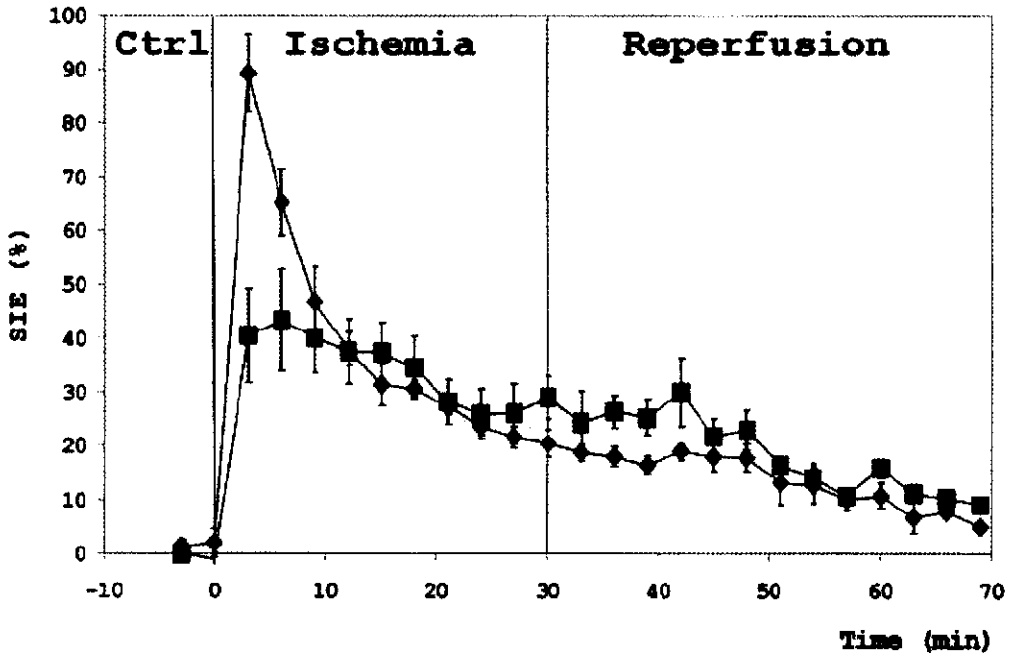


Figure 8b. see expl. Fig. 8c.

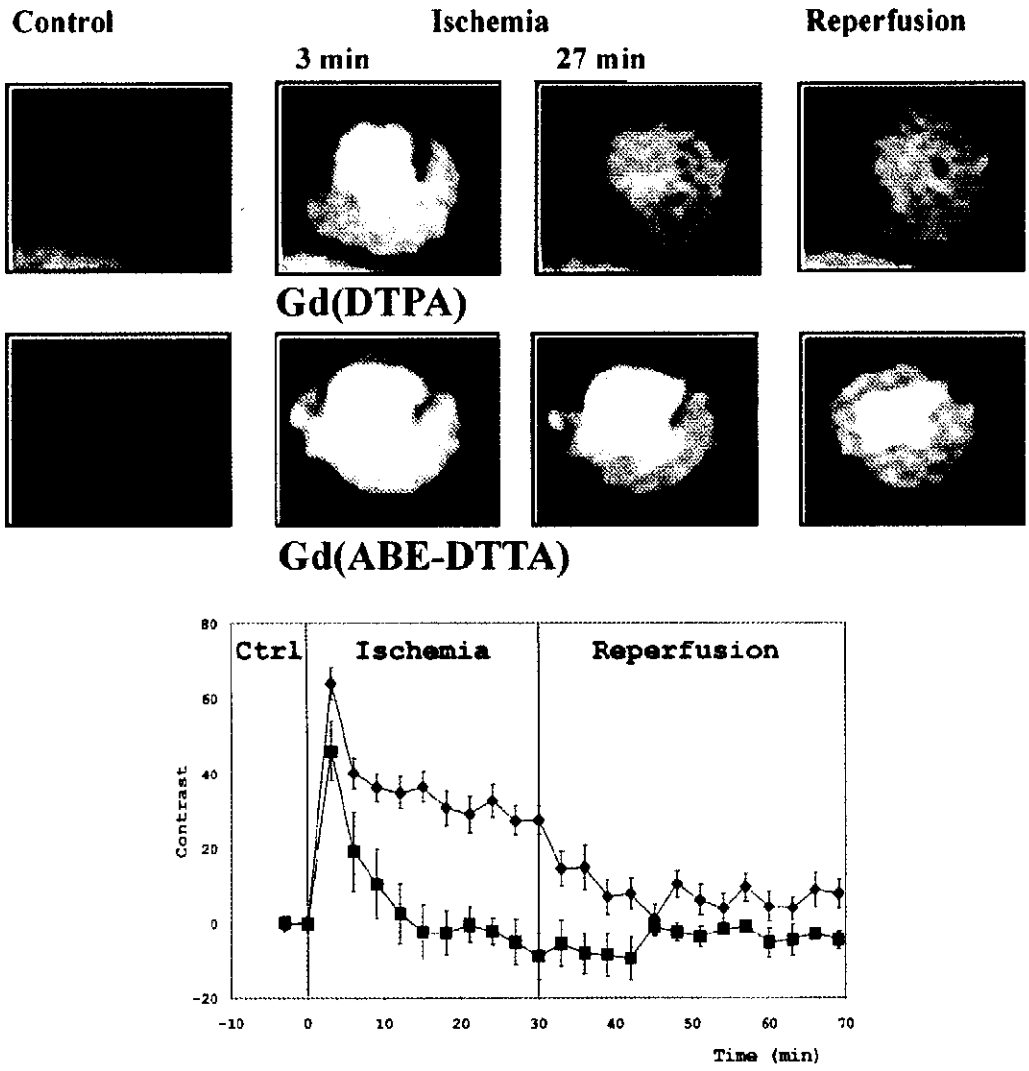
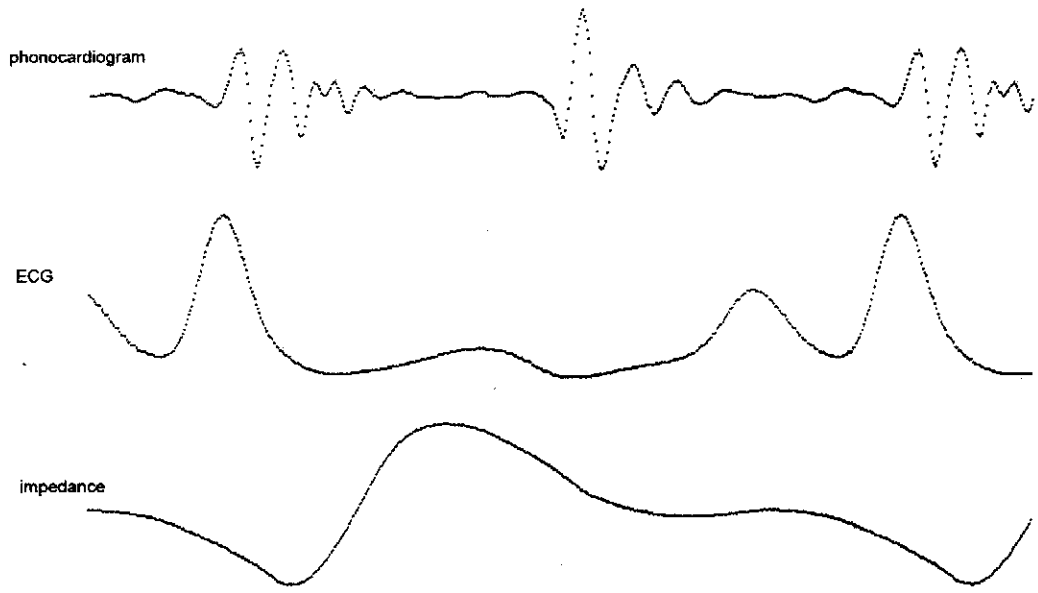


Figure 8c.

Time dependence of myocardial contrast in dogs a: Representative images from the control period, at 3 and 27 minutes of ischaemia and at 3 minutes of reperfusion are shown with either Gd(DTA) or Gd(ABE-DTTA). b: Contrast vs. time with Gd(ABE-DTTA) (N=6, diamonds) or with Gd(DTPA) (N=6, squares) were calculated from the data of Figs 8a and 8b respectively.



Curves of ICG. (phonocardiogram, ECG, baseline impedance)

Figure 9.

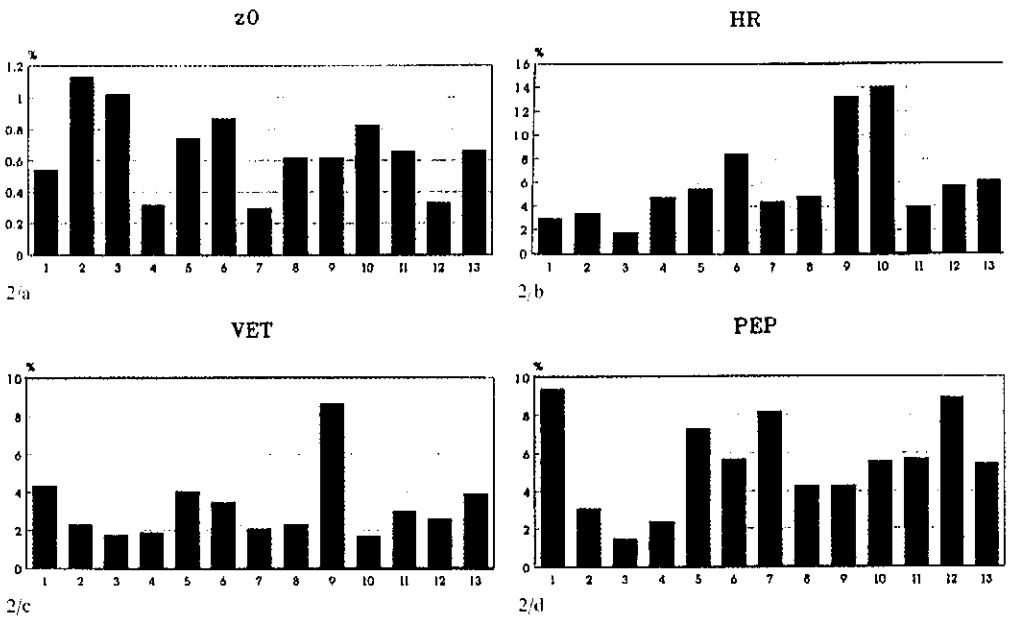
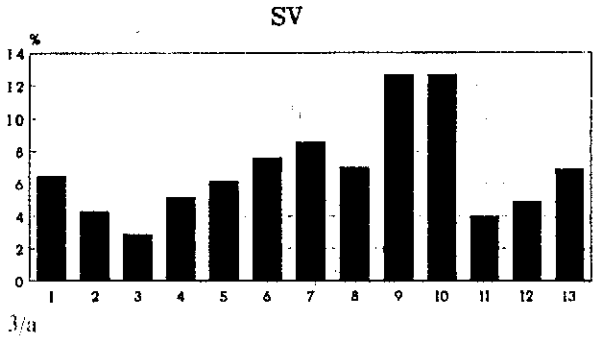
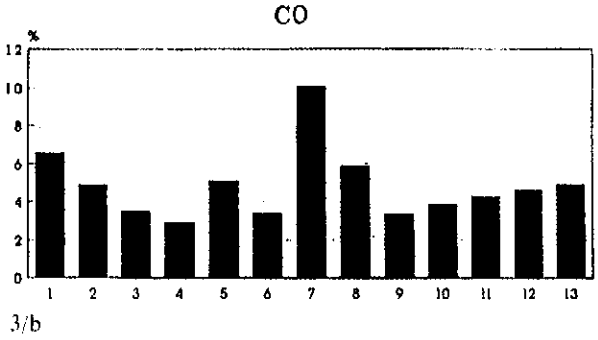

z0
%
1.2
1
0.8
0.6
0.4
0.2
0
1 2 3 4 5 6 7 8 9 10 11 12 13
2/a
HR
%
16
14
12
10
8
6
4
2
0
1 2 3 4 5 6 7 8 9 10 11 12 13
2/b
VET
%
10
8
6
4
2
0
1 2 3 4 5 6 7 8 9 10 11 12 13
2/c
PEP
%
10
8
6
4
2
0
1 2 3 4 5 6 7 8 9 10 11 12 13
2/d

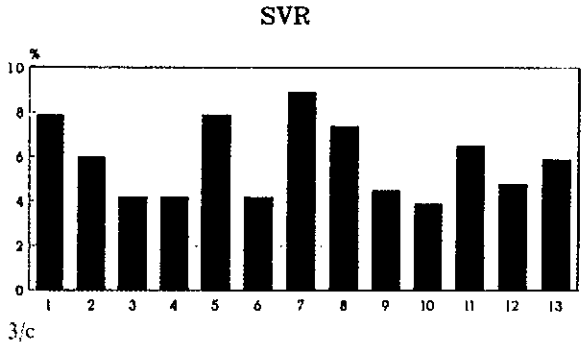
Fig. 10a.



3/a



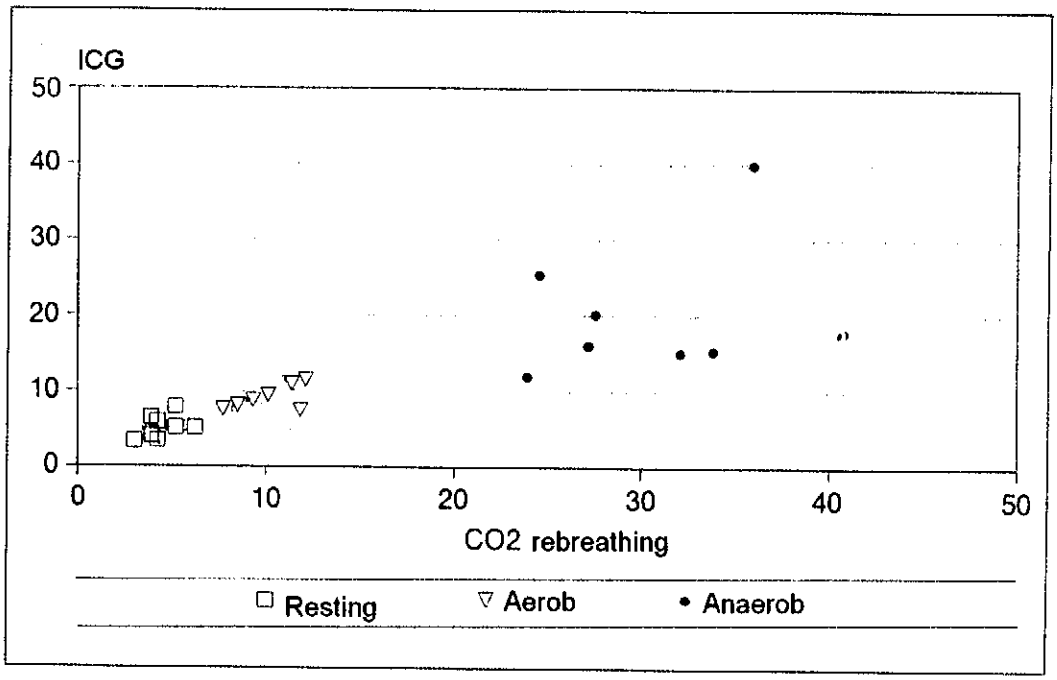
3/b



3/c

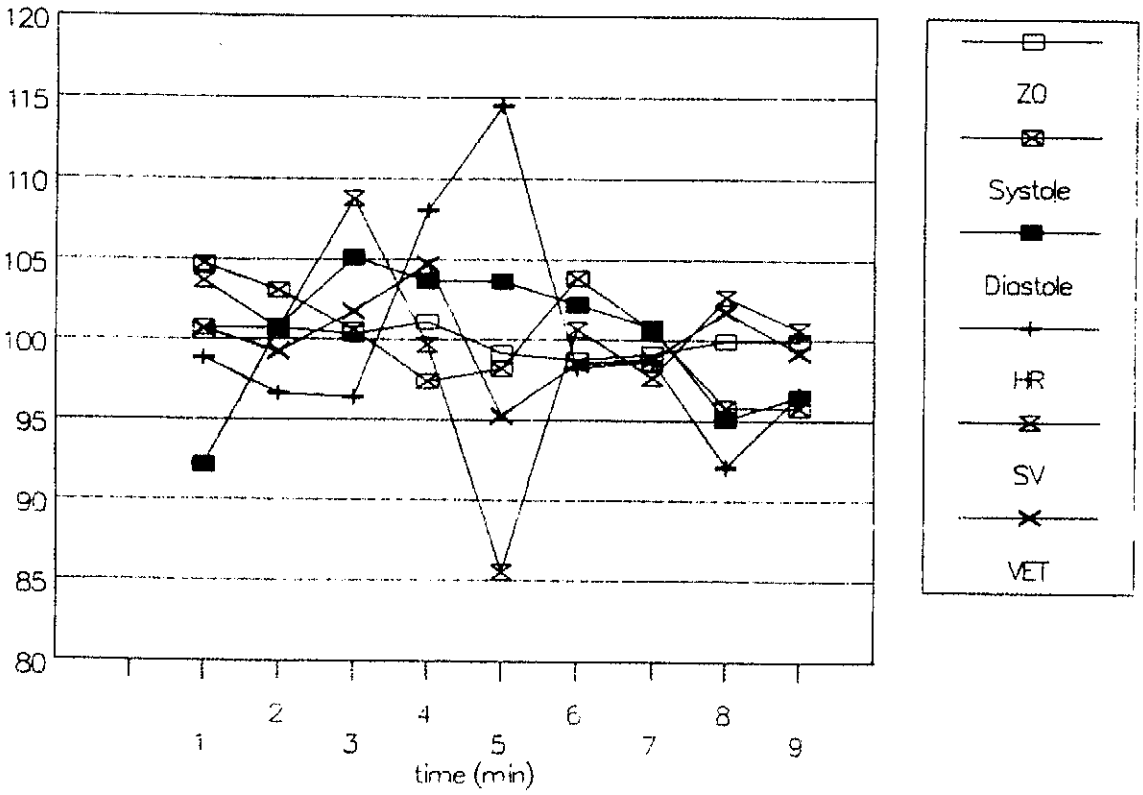
Stability measurements (Fig. 10a a-d and 10b a-c). N=12 pts, the 13. column is the average of the patients.

Figure 10b.



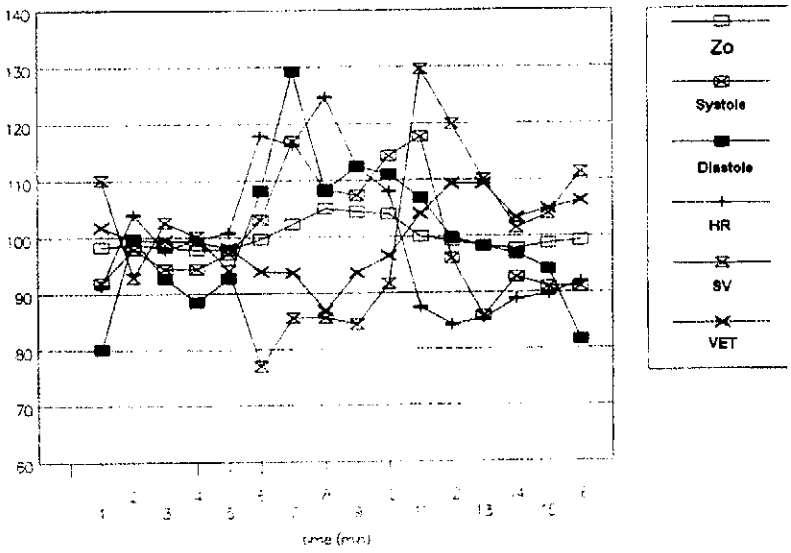
Cardiac output measurements during resting and exercise conditions (aerobic and anaerobic) The correlation coefficient during exercise is $r = 0.81$.

Figure 11.



Normal control patient CPT reaction.

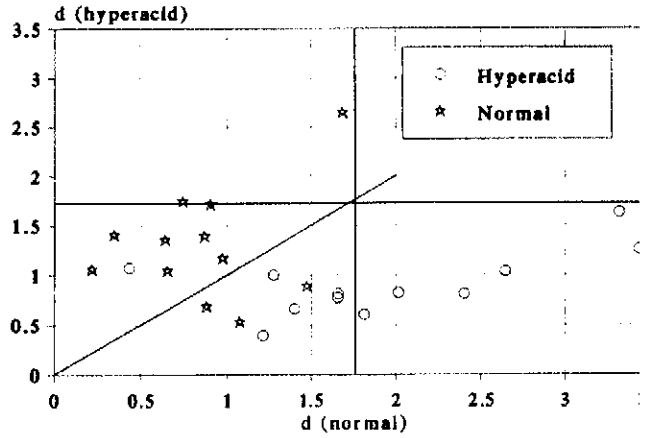
Figure 12.



Cold reaction of the hyperacid patient. After the stable phase (2–5 min) the long reactive period starts (6–13 min).

Hyperacid patient CPT reaction.

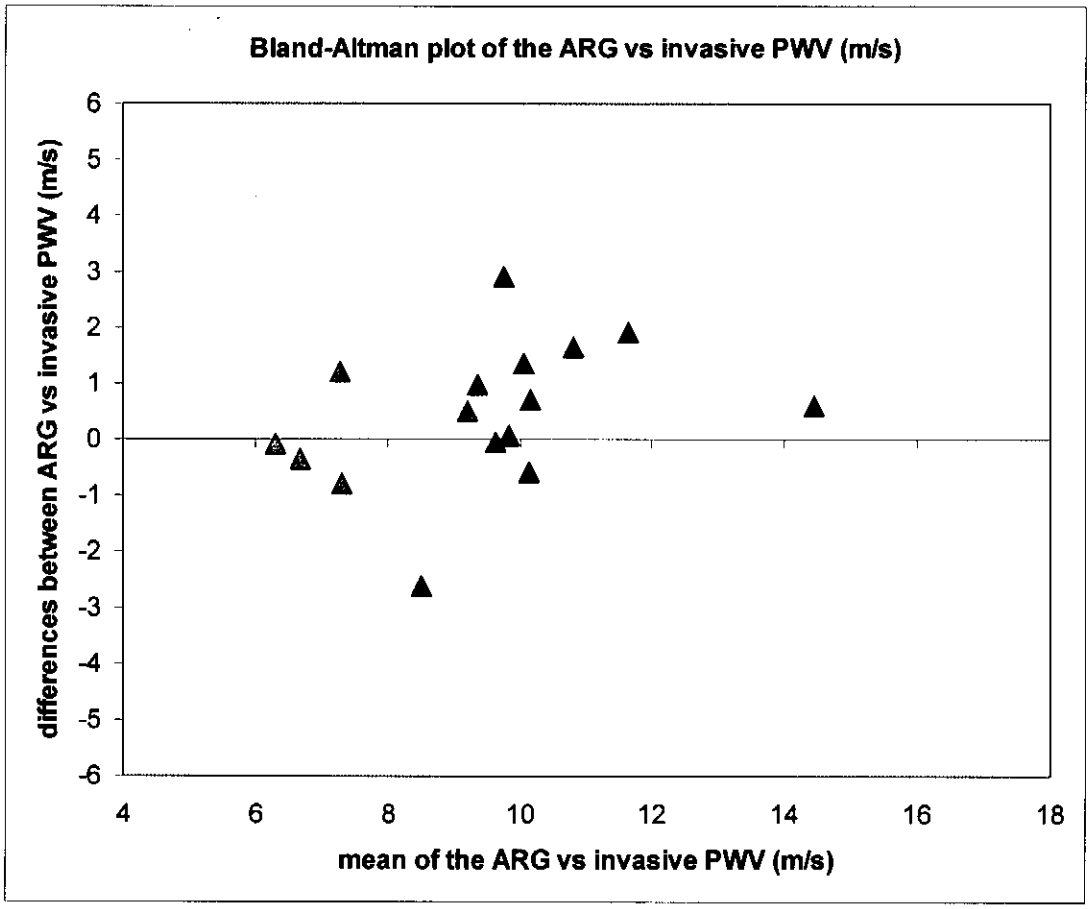
Figure 13.



The subjects were well separated by the multivariate statistical analyzing method (PRIMA) The x and y axis show the class distances ($n = 24$).

CPT-ICG-PRIMA method to separate different kind of patients CPT based hemodynamic changes depend on vascular reactions.

Figure 14.



Pulse wave velocity data measured by arteriograph non-invasively and at the same time invasively using diagnostic Judkins catheters.

Figure 15.

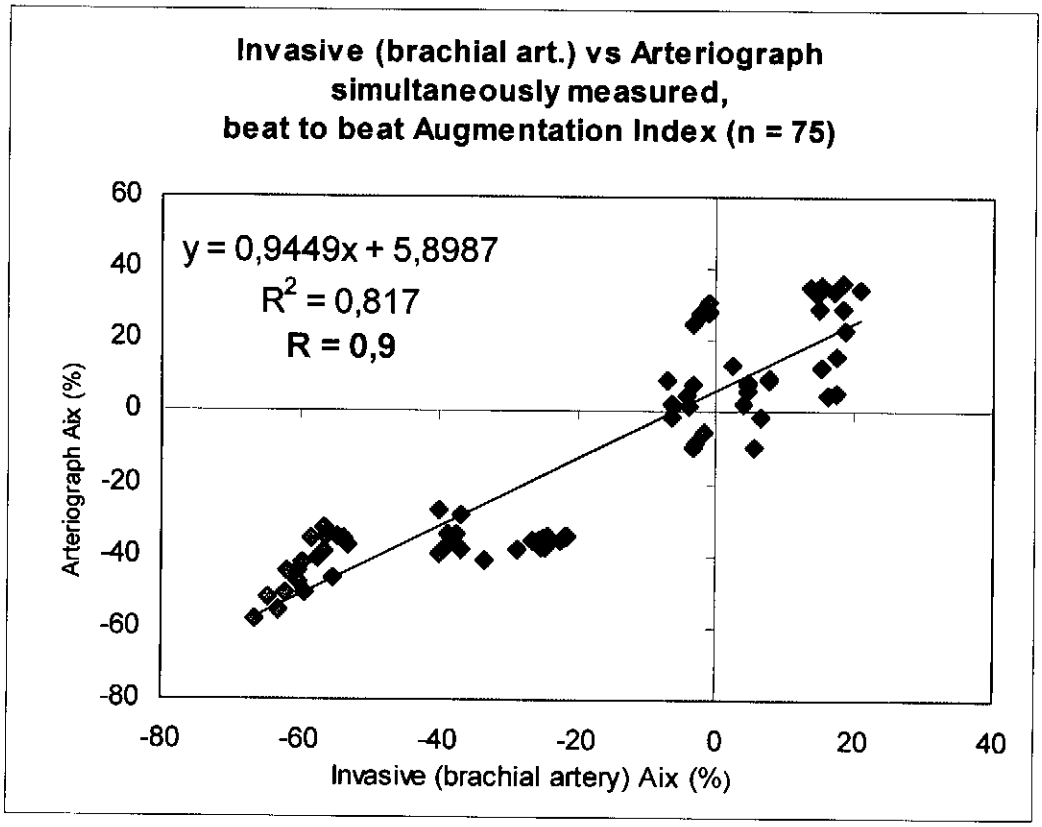

Invasive (brachial art.) vs Arteriograph
simultaneously measured,
beat to beat Augmentation Index (n = 75)
y = 0,9449x + 5,8987
R2 = 0,817
R = 0,9
Arteriograph Aix (%)
Invasive (brachial artery) Aix (%)
60
40
20
0
-20
-40
-60
-80
-80
-60
-40
-20
0
20
40

Figure 16.

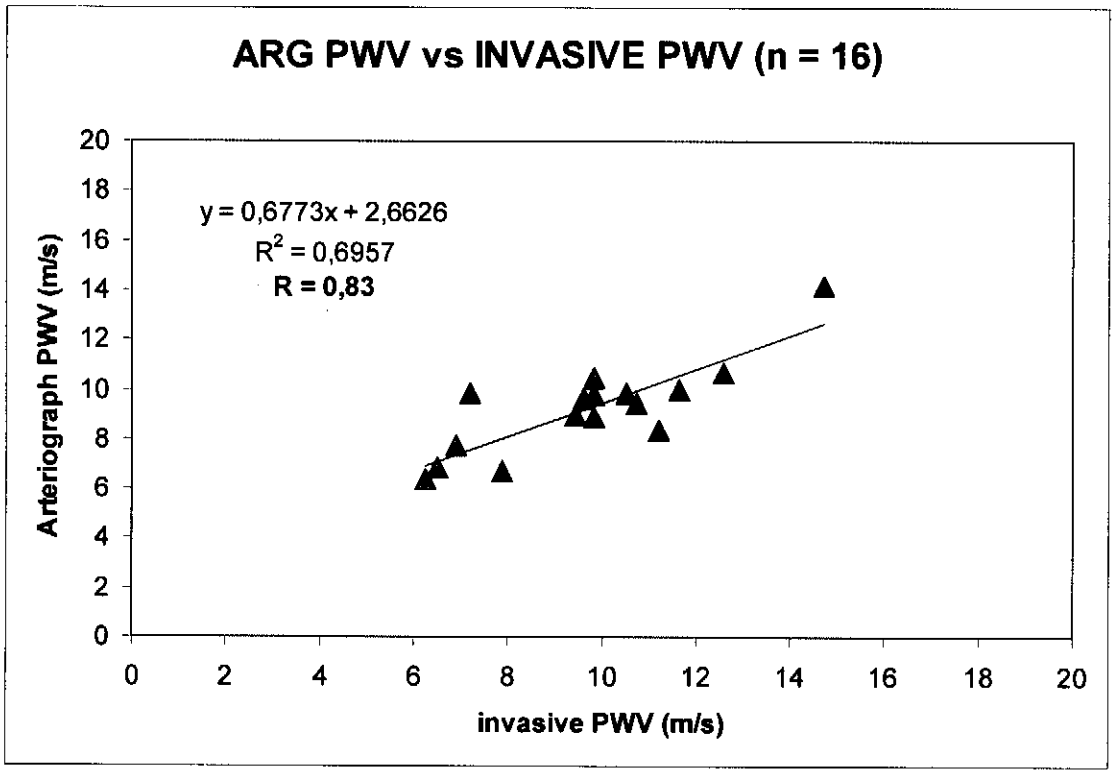

ARG PWV vs INVASIVE PWV (n = 16)
y = 0,6773x + 2,6626
R2 = 0,6957
R = 0,83
Arteriograph PWV (m/s)
invasive PWV (m/s)
0
2
4
6
8
10
12
14
16
18
20

Figure 17.

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István Juricskay PhD
Sami U. Kahn MD
Violetta Kékesi PhD
Pál Kiss MD
Béla Mezei MD, PhD
Gyula Mózsik MD, DSc
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