Biocybernetics and Biomedical Engineering
2008, Volume 28, Number 1, pp. 3–16

Interaction between Left Ventricle Mechanics and Myocardial Blood Flow

M. GIOVANNA TRIVELLA*, GUALTIERO PELOSI, DANILO NEGLIA, ANTONIO L'ABBATE[1]

C.N.R. Institute of Clinical Physiology, Pisa, Italy
[1] *Scuola Superiore Sant'Anna, Pisa, Italy*

The interaction between coronary circulation and left ventricular mechanics has been studied in animal models as well as investigated in humans. Here we review the results of experimental studies performed at the Institute of Clinical Physiology: the separate contribution of preload and afterload on coronary pressure-flow, pressure-volume and volume-flow relationships; single beat as well as averaged instantaneous loops, both during autoregulation and under maximal vasodilation. We then present the results of animal studies on estimate of functional microvascular architecture and its relationship with myocardial blood flow heterogeneity. Finally, we report on clinical applications performed in various models of left ventricular dysfunction as myocardial ischemia, hypertrophic cardiomyopathy, dilated cardiomyopathy and secondary hypertrophy, aimed at investigating the interaction between coronary flow and abnormal left ventricular mechanics.

K e y w o r d s: coronary circulation, left ventricular mechanics animal models, clinical studies

1. Introduction

Coronary circulation dynamics is strongly interrelated with the mechanics of the left ventricular contraction, relaxation, and filling. Interaction between coronary vasculature and the surrounding cardiac tissue primarily depends on transmural microvascular pressure and changes in ventricular geometry, mainly related to muscular fiber direction, collagen shortening and stretching. The intramyocardial flow is affected by the pump action of the contracting myocardium and its compressive forces on the intramural vasculature; these affect both vascular resistance and compliance according to the relationship between transmural pressure and vascular cross-sectional area.

* Correspondence to: M. Giovanna Trivella, C.N.R. Institute of Clinical Physiology, Via Moruzzi n. 1, 56124 Pisa, Italy, e-mail: trivella@ifc.cnr.it

It is well known that coronary flow at the arterial end is predominantly diastolic with only a small, sometime retrograde, systolic component while at the venous end it is exclusively systolic. The average intramyocardial flow is almost continuous, with very small changes throughout the cardiac cycle. Extravascular compressive pressure is a function of both intracavitary left ventricular pressure – linearly decreasing from endocardium to epicardium – and interstitial fluid pressure as depicted by the multilayer muscle-collagen model of the left ventricle [1]. At very low cavity pressure, a high myocardial tissue pressure can still be produced, due to significant muscle shortening and radial collagen stretching, as in small hearts with high ejection fraction, during catecholamine stimulation.

Myocardial perfusion is mainly controlled by the microvascular resistance and coronary driving pressure; whereas flow in superficial coronary arteries is dominated by both epicardial and intramyocardial arterial capacitance and by the local transmural pressure. The study of the interaction between left ventricular mechanics and myocardial blood flow can be performed in animal and in clinical models as well. With animal models the difficulties are: 1) animal care requirements, 2) application of numerous regulations and laws which limit the number of experiments, 3) absence of adequate pathological models, 4) difficulties in the induction of pathological states 5) substantial differences between animal and clinical models.

As an example, animal models of heart failure may largely vary according to the purpose(s) of a study: identifying and quantifying injured myocardium, assessing mechanisms of heart failure or its time course, testing and evaluating therapeutical interventions such as drugs or assist devices. In either case, many problems have to be faced. Increasing ventricular pressure or volume load is often insufficient to produce heart failure. To modulate the degree of heart failure by induction of myocardial necrosis is also a difficult task as this approach results in either a high mortality rate or more often in only a transient left ventricular dysfunction, depending on the animal species. High frequency ventricular pacing requires a long time for heart failure to develop and leads to functional recovery at interruption [2].

On the other hand, human cardiac diseases such as arterial hypertension, aortic stenosis, hypertrophic and dilated cardiomiopathies are suitable models for studying the interaction between coronary blood flow and ventricular mechanics; however clinical investigation in this field often contrasts with invasiveness of the procedures required and their ethical use.

The results from both animal and clinical studies will be presented in the attempt to clarify the relationship between coronary dynamics and cardiac mechanics.

2. Materials and Methods

This section reviews the techniques, methodologies, and study designs of experimental and clinical investigations.

In the anaesthetized open chest pig, during monitoring of ECG, aortic pressure, left ventricular pressure, left ventricular volume by conductance catheter and electromagnetic flow signal from left anterior descending coronary artery, a transient marked reduction of preload was performed by balloon caval occlusion. Before occlusion, the functional component of coronary resistance was abolished by intracoronary adenosine infusion and the increase in inotropic state induced by i.v. isoproterenol administration. Caval occlusion is a reproducible way of inducing changes in ventricular volume and pressure by progressive reduction of venous blood return to the heart. Continuous recording of the successive pressure/volume loops allows measuring and monitoring the left ventricle inotropism as well as its diastolic function. Furthermore, pressure/flow loops, obtained by arterial pressure and coronary blood flow instantaneous values, make it also possible to evaluate changes in coronary resistance within the single beat, in different haemodynamic conditions and at different left ventricular volumes. In this way the patterns of coronary resistance at different time intervals during autoregulation and during vasodilation induced by intracoronary adenosine infusion were analysed.

An increase in the left ventricle afterload has also been induced by transient aortic balloon inflation.

While the flowmeter signal from a large coronary artery provides information on instantaneous changes in total systolic and diastolic resistance throughout the cardiac cycle, the radioactive microsphere technique allows to assess specific (ml/min/g of tissue) myocardial blood flow and its distribution within the ventricular walls. The microsphere technique represents the gold standard for such measurements, although its spatial resolution is limited by the size of tissue samples. This limit can be overcome by computerized autoradiography which is, however, costly and time consuming.

Myocardial blood flow measurement by microspheres during increased left ventricular afterload can provide information on changes in coronary resistance in different layers and walls of the heart.

The combination of myocardial blood flow measurement by the radioactive microsphere with repetitive intracoronary injections of a known number of embolizing non radioactive microspheres of different sizes, makes it possible to derive a model of the functional architecture of coronary microvasculature. Such model is based on the relationship between the increase in minimal coronary resistance following embolization and the number and size of injected microspheres (Fig. 1).

As far as clinical studies are concerned, information on the relationship between coronary blood flow and perfusing pressure can be obtained by invasive techniques in the catheterization laboratory (Fig. 2) both during autoregulation and following vasodilation by i.v. administration of adenosine or dipyridamol.

By means of coronary and left ventricle catheterization, pressure-flow and pressure-volume loops can be obtained in different clinical models and in different haemodynamic conditions, using the Doppler flow signal as a sensor of myocardial mechanics.

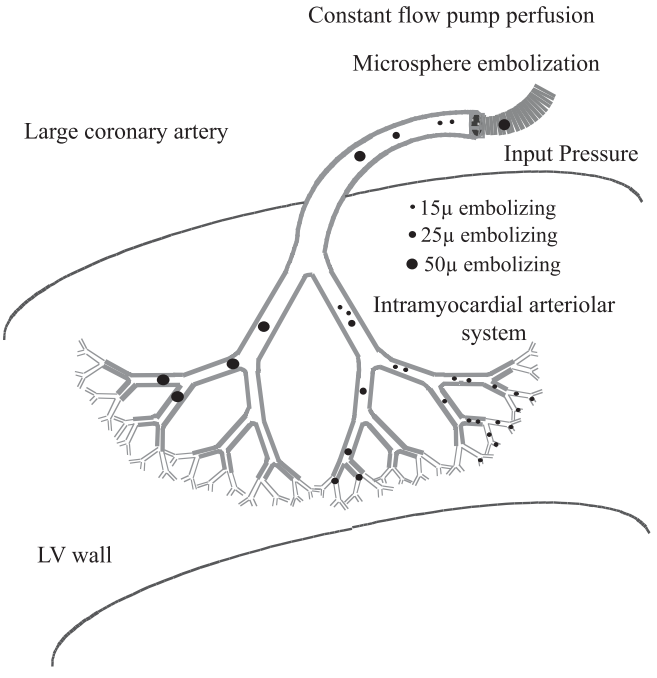

Fig. 1. Simplified scheme of a segment of the coronary arterial tree (from the epicardial large coronary artery to the arterioles). The experimental approach of the modelling of functional microvascular architecture based on the relationship between the increase in minimal resistance and the number of injected embolizing microspheres of known size is shown

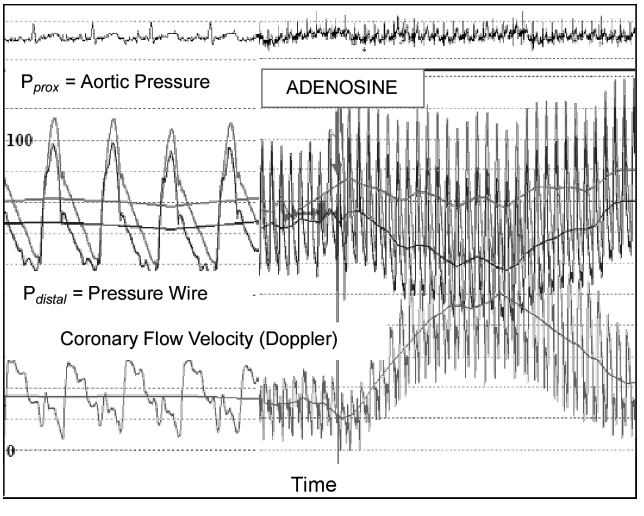

Fig. 2. The invasive monitoring of: from top to bottom, ECG, aortic and coronary pressures (phasic and mean, in mmHg) and the Doppler coronary flow velocity (phasic and mean, in cm/sec) from a normal subject, during autoregulation and after i.v. injection of adenosine (arrow). The signals on the right side of the panel are recorded by reducing the speed of the paper

Finally, a non invasive myocardial blood flow quantization and its distribution were obtained by Positron Emission Tomography (PET) in normal subjects and in clinical models of altered left ventricular mechanics and geometry.

3. Results

3.1. Experimental Studies

3.1.1. Instantaneous Pressure-flow and Flow-volume Loops: Effects of Preload Reduction and Afterload Increase

The coronary flow-pressure relationship, in autoregulation and during maximal vasodilation, can be analyzed during inflation and deflation of the vena cava balloon (preload modulation) using mean flow and pressure values (Fig. 3) as well as instantaneous values within a single cardiac cycle. The latter approach allows reconstructing of single beat flow-pressure loops both in autoregulation and during adenosine infusion. Within the loop it is possible to distinguish the systolic phase of the cardiac cycle with the pre-ejection and ejection periods as well as the diastolic phase characterized by the early sudden increase in flow during relaxation and its successive decline that parallels the decrease in aortic pressure (Fig. 4).

In the relationship between coronary flow and left ventricular volume, the sharp decline of flow during isometric contraction and its sudden increase during relaxation become evident (Fig. 5).

The analysis of phasic coronary flow signal during maximal vasodilation (Fig. 6) evidences that in baseline conditions flow has its minimum in the early systole when the wall stress is maximal and then starts to increase during ejection as the pressure

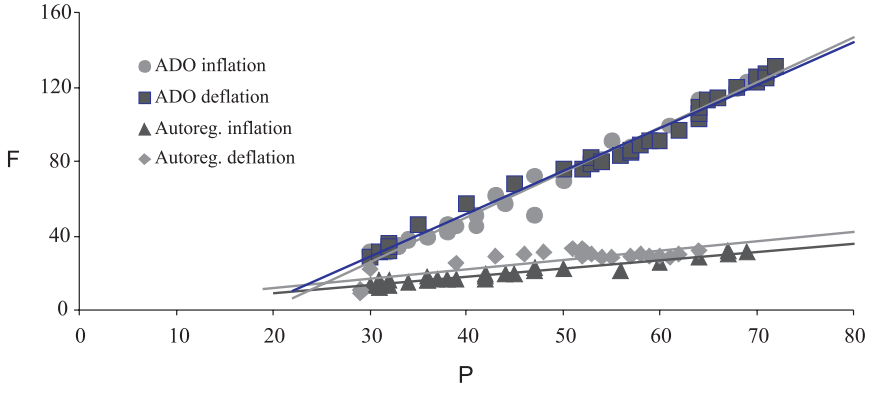

Fig. 3. The flow-pressure relationship (mean flow and pressure values) in autoregulation and during maximal vasodilation during inflation and deflation of the vena cava balloon (preload modulation). Pressure in mmHg, flow in ml/min

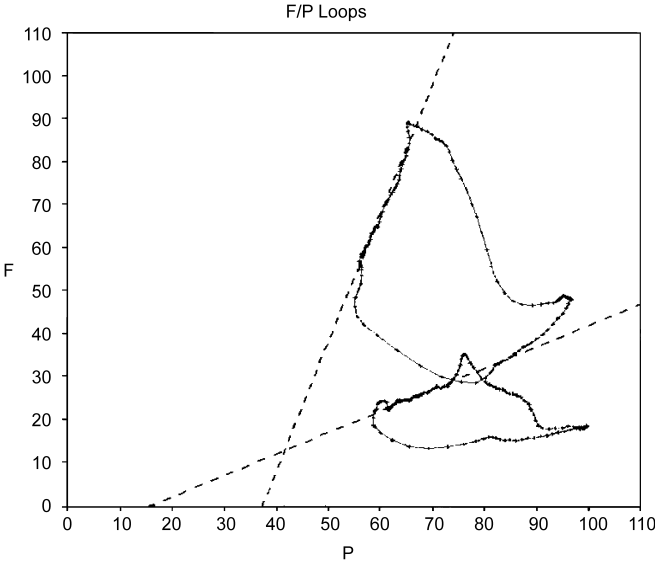

Fig. 4. The flow-pressure relationship within a single cardiac beat (flow-pressure loop) during adenosine infusion (above) and during autoregulation (below). Flow in ml/min, pressure in mmHg

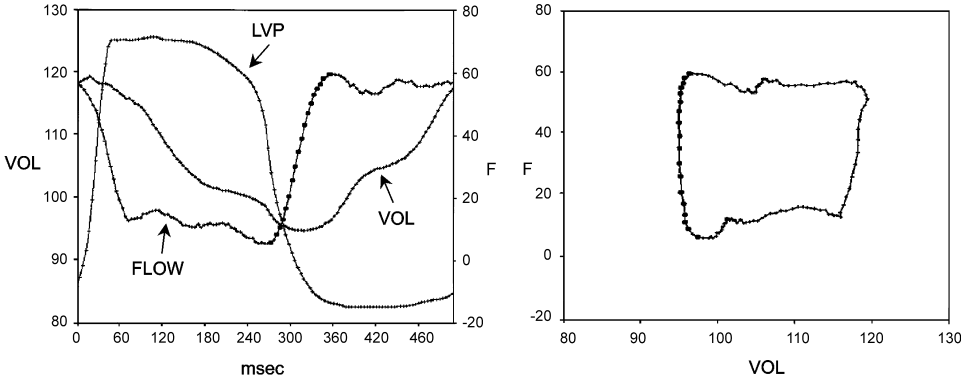

Fig. 5. Left: the instantaneous values of the coronary flow and the left ventricular pressure and volume during a single beat in autoregulation. Right: the corresponding flow-volume loop. Flow in ml/min, volume in ml

increases. By reducing the left ventricular pressure and the volume during caval occlusion, the minimal systolic flow point moves to midsystole when the systolic wall stress is no longer prevalent, while the ventricular volume reaches its minimum. On the other hand, diastolic flow peak is not only reduced by the decrease in aortic pressure but is also delayed toward the mid diastole.

Accordingly, profound changes in the shape of the flow-pressure loop occurs with a progressive shortening of the linear diastolic portion (Fig. 7) which can totally

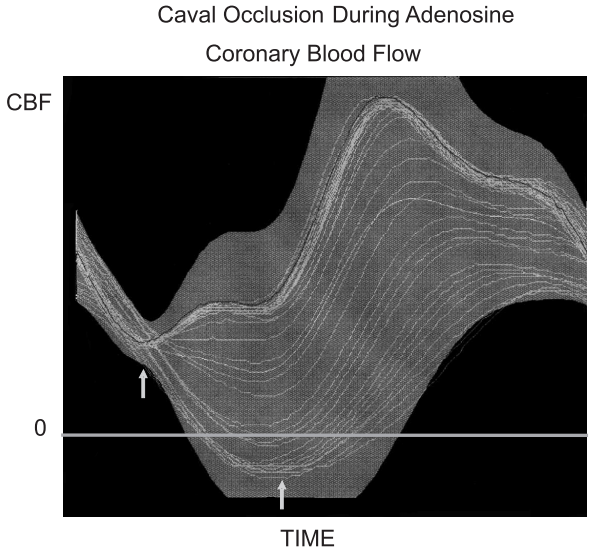

Fig. 6. The phasic coronary flow (CBF in ml/min; superimposed successive single cardiac beats) during maximal vasodilation (adenosine infusion) in the baseline conditions (minimum flow in early systole, left arrow) and during the caval occlusion (minimal flow in midsystole, right arrow)

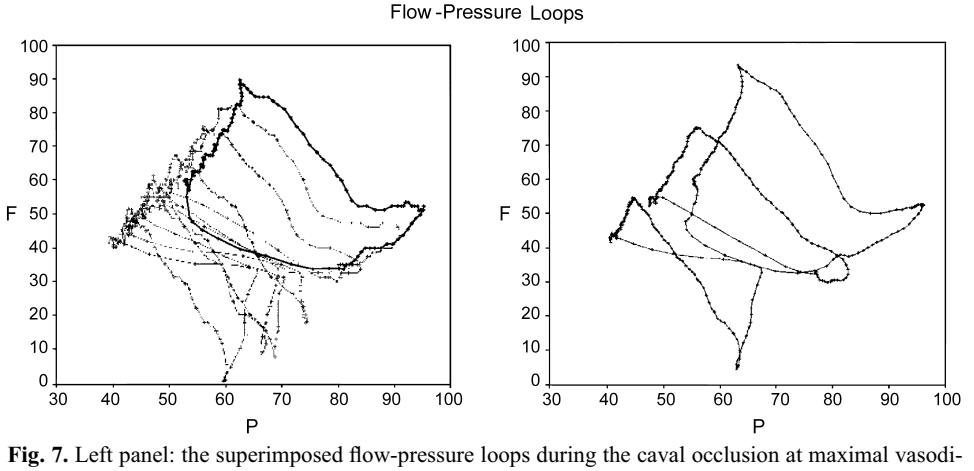

Fig. 7. Left panel: the superimposed flow-pressure loops during the caval occlusion at maximal vasodilation. Right panel: three representative loops from the beginning to the end (from top to bottom) of the caval occlusion showing the profound progressive loop distortion during preload reduction

disappear at very low pressure values (Fig. 8). On the other hand, the flow-volume loops show that, as left ventricular pressure and volume values decrease during caval occlusion, flow becomes more and more dependent upon the volume (Fig. 8). When even smaller volumes are obtained by isoproterenol injection, coronary flow becomes totally dependent upon the volume (Fig. 9).

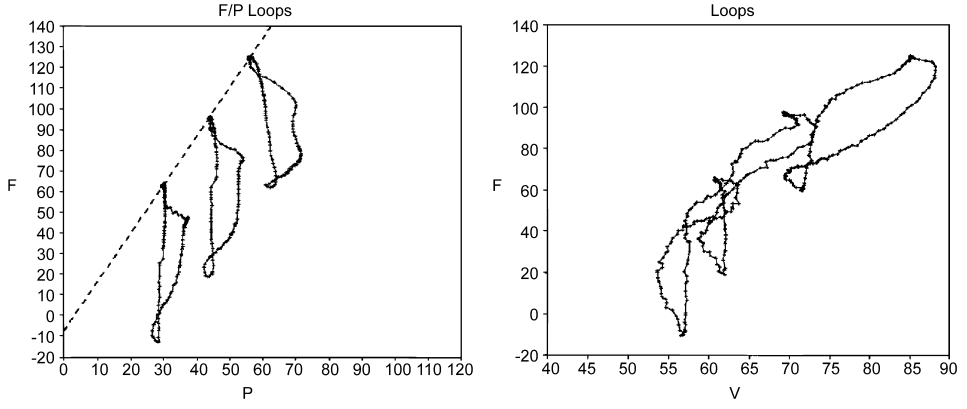

Fig. 8. The flow-pressure (left panel) and the flow-volume (right panel) loops during the maximal vasodilation, arterial hypotension and caval occlusion

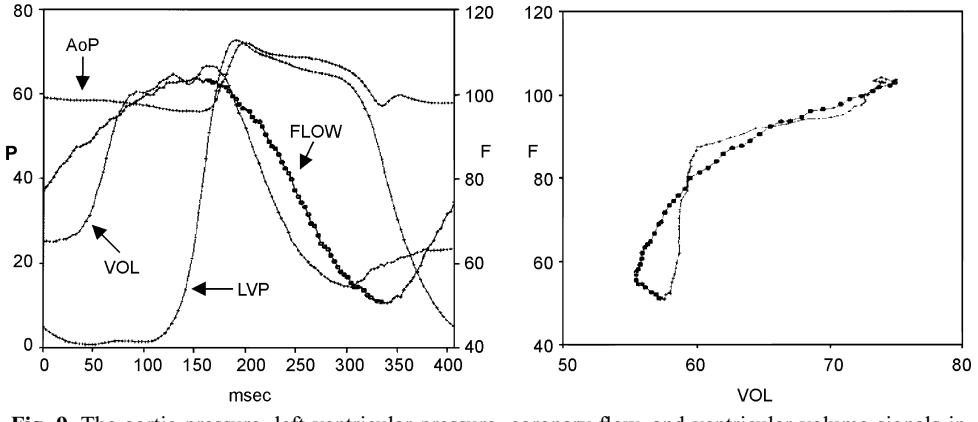

Fig. 9. The aortic pressure, left ventricular pressure, coronary flow, and ventricular volume signals in a single beat (left panel) and the corresponding flow-volume loop during isoproterenol injection. Note as the flow (ml/min) closely follows the volume (ml) changes

From the above findings we may conclude that coronary flow modulation throughout the cardiac cycle seems to be dependent on systolic wall stress during contraction and on isometric relaxation of the left ventricle in baseline physiologic state, whereas it becomes mainly dependent on volume changes at low ventricular pressure and small volume conditions regardless of the presence of autoregulation.

When afterload is increased by aortic balloon inflation, systolic flow reaches its minimum in early systole in the pre-ejection phase, totally depending on wall stress. During balloon deflation to the normal pressure condition, minimal systolic flow shifts to the late systole when wall stress is not prevalent, elastance is maximal, and volume is at its minimum value.

3.1.2. Transmural Myocardial Blood Flow Assessment

Regional pressure-flow relations of different myocardial wall layers, such as the subepicardial and subendocardial thirds of the left ventricular wall, can be obtained by microsphere technique in different physiologic conditions, during autoregulation and maximal vasodilation and at different left ventricular pressures. When vascular tone is abolished by vasodilators, pressure-flow relation is the only method for assessing the vascular anatomical and extravascular components of coronary resistances. The epi (epicardium) and endo (endocardium) pressure-flow relations at maximal vasodilation can be interpolated by linear regressions crossing each other at the normal value of coronary pressure. In correspondence of the crossing point flow is evenly distributed across the left ventricular wall [3].

When left ventricular pressure is increased, the systolic resistance increases and the crossing point is reached at higher coronary pressures, indicating that blood flow homogeneity can be maintained by higher driving pressure as wall stress increases (Fig. 10).

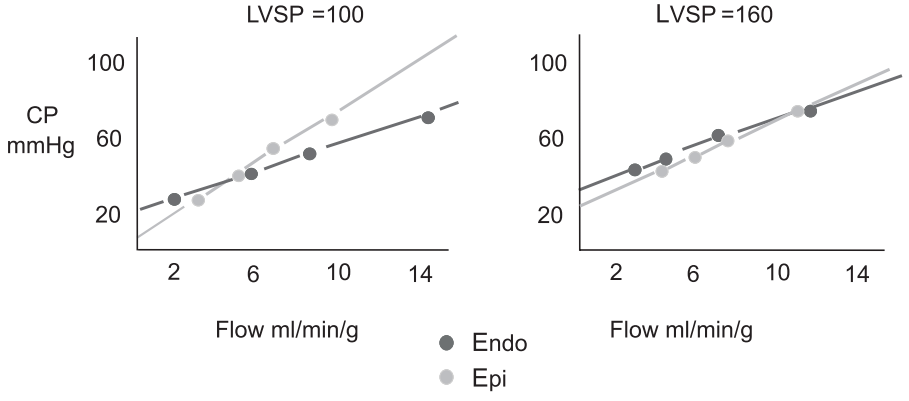

Fig. 10. The transmural (epicardial, grey dots and endocardial, black dots) pressure-flow relationships (mean data) during maximal vasodilation at the different values of the left ventricular systolic pressure (100mmHg, left panel; 160mmHg, right panel)

The relationship between transmural microvascular resistance and ventricular afterload (ventricular systolic pressure) shows that during maximal vasodilation the average coronary resistances of the endocardial layer are unchanged whilst those of the epicardium tend to decrease (Fig. 11).

With the radioactive microsphere technique, a substantial improvement in spatial resolution can be achieved by the computerized autoradiographic detection and mapping of microsphere distribution within few micron-thick transverse myocardial slices (Fig. 12). With such a spatial resolution, it become possible, by applying fractal

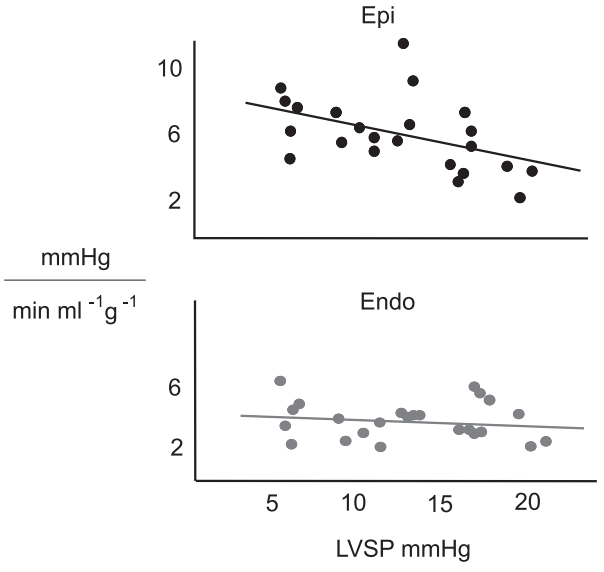

Fig. 11. The minimal average coronary resistances of the epicardial (above) and endocardial (below) layers at the different afterload levels (from 50 to 200 mmHg of the left ventricular systolic pressure)

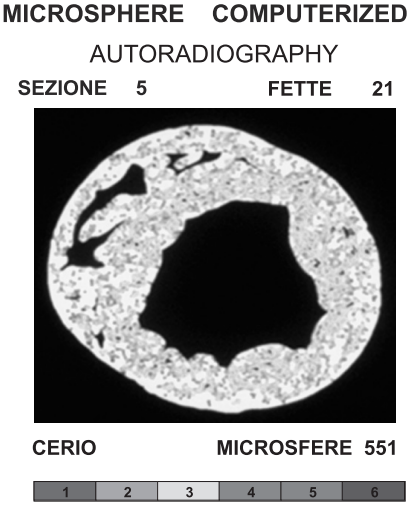

Fig. 12. The computerized autoradiographic mapping of the microsphere distribution in a transverse section of the heart. A sufficient number of microspheres was reached by adding the microsphere content of 21 sequential microslices (20 microns thick)

analysis, to reach a statistically significant blood flow assessment in myocardial regions as small as 1 mg which can be considered the functional microvascular units [4, 5].

3.1.3. Microembolization Studies

The intramyocardial arteriolar tree distal to 100μm diameter vessels is known to account for more than 50% of total coronary resistance therefore playing a primary role in modulating blood flow supply to the capillary network and in regulating the myocardial perfusion and its heterogeneity across the left ventricular wall. By assuming that embolizing microspheres distribute according to flow and occlude vessels of the similar size, the relation between the increase in total coronary resistance induced by the vascular occlusion and the number of vessels progressively embolized – "occlusion function" – is determined both by the architecture and the single vessel resistance values of the coronary arteriolar tree. Using this approach, the intramyocardial arteriolar tree is transmurally heterogeneous [6] with a greater total vascular cross section in the endo as compared to epi layers. Moreover, the relation between the microvascular pressure at a certain level and increase in the total resistance following 50% vascular occlusion of that level could also be defined. The model equation which correlates the number of branching levels to the relative increase in global and transmural (endocardial and epicardial) resistance following 50% vessels occlusion at four branching orders has been applied to the occlusion functions obtained by 15 μm, 25 μm, 55 μm and 100 μm vessels embolization with plastic spheres in the maximally dilated circumflex artery of the dog. A regular binary branching tree with 8 branching orders downstream 100 μm vessels and with a terminal arteriolar density in the subendocardium double than in the subepicardium was found adequate to fit the embolization results. The intravascular pressure prediction was found close to the experimental measurements downstream 100 μm diameter arterioles [7].

Analysing of the effect of microvascular geometry patterns on coronary circulatory dynamics could help clarify the interplay between function and structure in the coronary microcirculatory system [8].

3.2. Clinical Studies

In normal subjects, coronary flow-pressure loops obtained during catheterization by intracoronary continuous recording of Doppler signal are similar to those obtained in animal models both during autoregulation and during adenosine infusion. In patients with coronary stenosis which does not create a measurable pressure gradient across the obstruction under autoregulatory state, adenosine infusion can induce a vasodilation of the vasculature downstream the stenosis and determine a pressure gradient which can be measured as an index of possible myocardial ischemia at increased oxygen demand.

Doppler coronary blood flow velocity can be obtained also non invasively by trans-thoracic or trans-oesophageal echodoppler usually by visualizing the medial portion of the left descending coronary artery. The simultaneous assessment of flow velocity and coronary cross sectional area allows to obtain reliable flow measurements

both in basal conditions and following adenosine or dipyridamol i.v. administration, thus allowing the estimation of the coronary flow reserve. In humans, the coronary reserve is considered normal when, at a stable perfusion pressure, vasodilation at least doubles the baseline value. The assessment of coronary reserve by the Doppler approach, although limited to the sole district of the explored coronary branch, is an important diagnostic tool as the prerequisite for the occurrence of myocardial ischemia when the increased in myocardial oxygen demand cannot be matched by a parallel flow increase. Regional coronary reserve in the context of the global left ventricle can be assessed non invasively by several techniques such as ECHO contrast, SPECT and NMR, using flow tracers. However, these techniques, while providing information on myocardial blood flow distribution within the left ventricular walls, do not quantify the flow. This important limitation can be overcome by Positron Emission Tomography (PET) the only available technique able at the same time to provide imaging and quantitative estimation of myocardial perfusion.

Using the PET we studied the relationship between myocardial perfusion and ventricular function in several clinical models characterized by ventricular symmetrical, such as arterial hypertension or aortic valve stenosis, or asymmetrical hypertrophy as in hypertrophic cardiomyopathy, or by ventricular dilation and systolic dysfunction such as in the idiopathic dilated cardiomiopathy. Unexpectedly, in these studies we have frequently observed severe regional perfusion abnormalities not related to coronary obstructive lesions, as those typical of ischemic heart disease, nor to the presence or geometrical distribution of myocardial hypertrophy [11]. Figure 13 shows a paradigmatic example of regional impairment of perfusion in two patients with severe aortic valve stenosis but normal coronary arteries.

Finally, the reconstruction of the flow-pressure loop from the aortic pressure and the coronary Doppler flow velocity signals obtained in patients with ventricular

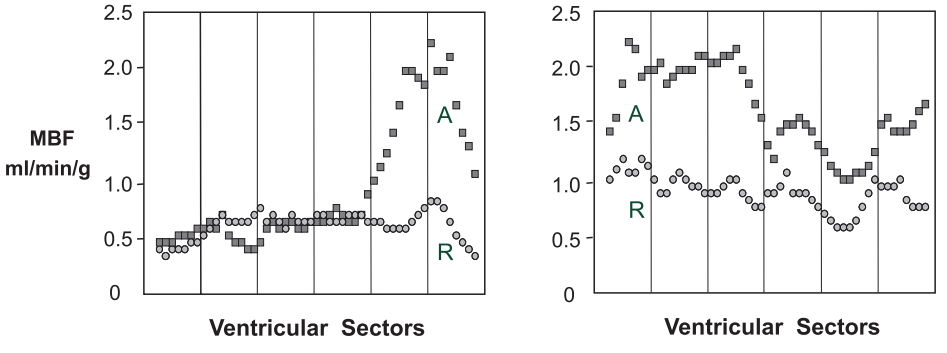

Fig. 13. The non invasive *in vivo* quantization of the myocardial blood flow (MBF) at the rest (R, circles) and following the adenosine (A, squares) in two patients affected by the secondary myocardial hypertrophy (aortic valve stenosis) using PET. In each panel, ventricular sectors refer to a single left ventricular slice and go, left to right, from the lateral wall to the interventricular septum. Impairment of the coronary flow reserve (no or slight increment of the flow following adenosine as compared to resting) in large portions of the ventricle can be appreciated in both patients

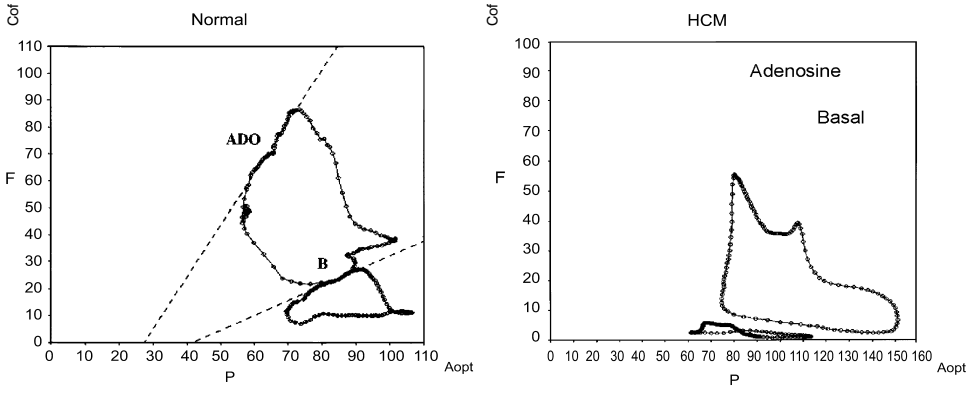

Fig. 14. The flow-pressure loops at the baseline (bottom) and during the adenosine infusion (top) obtained during catheterization in a normal subject (left panel) and in a patient with the hypertrophic cardiomyopathy (right panel)

structural and functional alterations seem to support the view that phasic flow signal contains important information on the ventricular mechanics during systole and diastole. Figure 14 illustrates the profound deformation of the flow-pressure loops obtained in baseline conditions and following adenosine in a patient with hypertrophic cardiomyopathy as compared to those obtained in a normal subject.

4. Conclusions

When comparing the experimental and clinical studies on the interaction of coronary flow with left ventricular mechanics we must be aware of several differences of great pathophysiological relevance.

Despite the different data available due to the less invasive techniques applicable in humans, giving often qualitative and/or semiquantitative measurements, the flow-pressure loops seem to be the investigation mean for studying the interrelations between myocardial flow and coronary mechanics, with the systolic flow behaving as a sensor of the wall contraction and the flow sudden increase that one of the relaxation.

Finally, we must consider that the natural history and the chronicity of the diseases by reaching a progressive new “equilibrium” or homeostasis could be the main factors of the differences among experimental and clinical data.

Acknowledgments

We thanks Graziano Barsotti for the precious assistance in figure preparations.

References

1. Beyar R., Caminker R., Manor D., Sideman S.: Coronary flow patterns in normal and ischemic hearts: transmyocardial and artery to vein distribution. Ann. Biomed. Eng. 1993, 21, 4, 435–458.
2. Trivella M.G., Del Canizo J.F., Chieco S., Flameng W., Meli M., Meyns B., Monties J.R., Waldenberger F., Rakhorst G.: Guidelines for in-vivo testing of mechanical circulatory support systems. Report Concerted Action Heart Assist and Replacement, Section III — ISBN 88 - 86219.05.09, III-1 - III-40, 1996.
3. L'Abbate A., Marzilli M., Ballestra A.M., Camici P., Trivella M.G., Pelosi G., Klassen G.A.: Opposite transmural gradients of coronary resistance and extravascular pressure in the working dog's heart. Cardiovascular. Res. 1980, 14, 21–29.
4. Bassingthwaighte J.B., King R.B., Roger S.A.: Fractal nature of regional myocardial blood flow heterogeneity. Circulation Research 1989, 65, 578–590.
5. Trivella M.G., Castellari M., Pelosi G., Barsotti G., Magnozzi D., Taddei L., Balocchi R., Marchesi C., L'Abbate A.: Microvascular perfusion unit visualized by computerized autoradiography of canine myocardium. Proceedings of Sixth World Congress for Microcirculation, Messmer K., Kubler W. M.(Eds), Monduzzi 1996, 851–855.
6. Pelosi G., Saviozzi G., Trivella M.G., L'Abbate A.: Transmural redistribution of coronary resistance during embolization: a clue to intramyocardial small artery architecture. Microvascular Research 1990, 39, 322–340.
7. Pelosi G., Saviozzi G., Trivella M.G., L'Abbate A.: Modeling of the intramyocardial canine microcirculation by small artery embolization. 6th World Congress for Microcirculation, K. Messmer, W. M. Kubler (Eds), Monduzzi 1996, 191–195.
8. Kassab G. S.: Scaling laws of vascular trees: of form and function. Am. J. Physiol. Heart Circ. Physiol. 2006, 290, H894-H903.
9. Trivella M.G., Castellari M., Pelosi G., Barsotti G., Magnozzi D., Taddei L., Balocchi R., Marchesi C., L'Abbate A.: Microvascular perfusion unit visualized by computerized autoradiography of canine myocardium. 6th World Congress for Microcirculation, K. Messmer, W. M. Kubler (Eds), Monduzzi 1996, 851–855.
10. Trivella M.G., Pelosi G.: Coronary Microcirculation. In: Textbook of Angiology, Chang J. B. (Ed), Springer-Verlag, New York, USA, 2000, 132–140.
11. Gimelli A., Schneider-Eicke J., Neglia D., Sambuceti G., Giorgetti A., Bigalli G., Parodi G., Pedrinelli R., Parodi O.: Homogeneously reduced versus regionally impaired myocardial blood flow in hypertensive patients: two different patterns of myocardial perfusion associated with degree of hypertrophy. J. Am. Coll. Cardiol. 1998, 31, 366–373.