Exercise in lambs with an aortopulmonary left-to-right shunt
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1993

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Summary

Introduction (Chapter 1)

Congenital heart defects resulting in a left-to-right shunt and left ventricular volume loading are accompanied by increased myocardial work. Specifically, the enlarged end-diastolic volume and stroke volume augment left ventricular wall stress and external work, respectively; heart rate is increased to raise left ventricular output and compensate for the runoff through the shunt; and contractility is often increased due to the elevated plasma concentration of catecholamines. In a previous study, it was demonstrated that resting myocardial blood flow and oxygen consumption are increased in lambs with a left-to-right shunt due to the augmented cardiac work. This finding forms the basis for the studies in the present thesis.

During increased circulatory demand, such as occurs during feeding, crying, or physical activity, there is an increase in myocardial work load and, hence, in oxygen demand. Coronary blood flow must follow, but because it is increased at rest and because maximum coronary blood flow is probably not higher than in individuals without a shunt, coronary blood flow reserve is decreased, so that myocardial oxygen demand may not always be met. This could result in ischemic myocardial injury, with negative consequences for cardiac function, in the short or long term, which would put the attitude of waiting for spontaneous closure of the defect in a different perspective (Chapter 5).

The enhanced myocardial oxygen consumption is mainly due to an increase of cardiac work. In addition, increased catecholamine concentrations may also play a role, not only because of their effect on contractility and basal metabolism, but also because they have been demonstrated to enhance myocardial fatty acid utilization. Fatty acids require more oxygen during oxidative phosphorylation to produce the same amount of ATP as compared with glucose, which is unfavorable in view of their probably decreased coronary reserve. Fatty acid utilization could further increase during additional work, with further elevation of catecholamine concentrations, or during treatment of such infants with catecholamines (Chapters 6, 7, and 10).

The threefold increase in resting coronary blood flow must be accompanied by a redistribution of systemic blood flow because systemic blood flow is not different from that in individuals without a shunt. If this is established at the cost of a decrease in splanchnic blood flow, as observed in adults with ischemic heart failure, it could interfere with gastrointestinal function and contribute to the failure to thrive in infants with left-to-right shunts (Chapter 4).

Adults with volume loaded hearts often have a decreased myocardial function. The lower exercise capacity of children with a left-to-right shunt compared with children without heart disease could indicate that this is also the case in infants. However, hemodynamic measurements at the maximum exercise level have not yet been made. Since infants are not yet full-grown they may, in contrast to adults, be able to adapt more favorably to the volume load (Chapter 3).
Isoproterenol can be used for children that cannot cooperate in the exercise stress test used in the evaluation of heart patients. Compared with exercise, isoproterenol does not induce an increase in systemic blood pressure, so that cardiac workload during an isoproterenol stress test may be lower than during exercise. In order not to underestimate the severity of an infant's heart disease, comparative data on cardiac workload during the two tests should become available (Chapter 8).

Isoproterenol is often used as a drug to enhance systemic blood flow. Data indicating which organs benefit from the increase of systemic blood flow in individuals with shunts are not yet available (Chapter 9).

Treatment of symptomatic children with left-to-right shunts has always been based on the policy for adults with heart failure, amongst others, consisting of diuretics and contractility enhancing agents. In the last decade it has become clear that the pathophysiology of newborns with congenital heart disease differs at certain points from adults. Contractility is usually good in the young. In fact, administration of digoxin to infants with ventricular septal defects has not been shown to improve their hemodynamic values. Furthermore, the retention of fluid by the kidneys may not be deleterious if myocardial function is preserved because it could increase systemic venous pressure and enhance the Frank-Starling mechanism. Edema, as a sign of in excess retained fluid, is rarely observed in infants, so that the expulsion of fluid may interfere with a potentially beneficial adaptation (Chapter 11).

Methods (Chapter 2)

The experimental left-to-right shunt was created in 5-week-old lambs by suturing a 6 mm Goretex conduit between the aorta and pulmonary artery. During the operation flow meters were placed around the aorta and pulmonary artery, and catheters were inserted into the aorta, pulmonary artery, right ventricle, left and right atrium, and coronary sinus. Half of the lambs did not receive a conduit during operation and served as the control group.

There were two study protocols: the exercise/isoproterenol protocol (23 lambs) and the body fluid compartment protocol (20 lambs). The lambs were studied two weeks after surgery. The lambs of the first protocol were familiarized with running on a treadmill in the week before surgery. Two lambs that refused to run could yet be included in the series by placing a mirror in front of them in which they recognized a congener so that they stayed in front of the mirror and so turned into willing runners once the treadmill was started.

The exercise study consisted of a 10 min treadmill run at 80% of maximum exercise capacity, which had been determined three days before during a grade treadmill test. Isoproterenol was infused during 15 min at a dose of 0.1 μg·kg⁻¹·min⁻¹.

The body fluid compartments were measured by means of a single injection, triple indicator dilution method.

Results and discussion

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During the increased circulatory demand of a 10-minute-treadmill run at 80% of maximum aerobic power, the heart still received a twice as large fraction of systemic blood flow, but this did not enhance the exercise-induced redistribution of systemic blood flow which reduced blood flow to the abdominal organs by 25%. Myocardial oxygen demand during strenuous exercise was no different from control lambs and could be met despite the decreased coronary blood flow reserve (Chapter five). This followed from the comparable increases in variables that set the determinants of myocardial oxygen consumption in the two groups, and the smaller increase in heart rate of the shunt lambs. An important factor was the 25% hypertrophy in the shunt lambs which reduced the volume load-induced increased myocardial oxygen demand per beat to normal levels, not only at rest but also during the additional load of strenuous exercise. Indications were also obtained that the myocardial hypertrophy was accompanied by capillary hyperplasia. Despite the increased end-diastolic left ventricular and aortic diastolic pressures, subendocardial myocardial blood flow in the shunt lambs was not compromised compared to control lambs.

Myocardial fatty acid uptake was similar in the two groups at rest and covered half of the energy metabolism (Chapter six). Resting lactate uptake of the shunt lambs was increased. This probably accompanied the increased myocardial work through enhanced pyruvate and lactate dehydrogenases. During the added work load of exercise the myocardium augmented its lactate utilization, so that it covered nearly half of its substrate consumption; lactate being abundantly present in the blood during exercise (Chapter seven). Also during exercise, there was no difference in fatty acid uptake between the two groups. Myocardial metabolism thus does not seem to play a part in enhancing myocardial oxygen consumption in individuals with a left-to-right shunt.
**Isoproterenol infusion** induced changes similar to exercise in systemic, pulmonary, and, which is noteworthy, also in shunt blood flow (Chapter eight). It did so better than in control lambs because the stroke volume of the shunt lambs was not affected by the decrease in ventricular filling pressure. It can thus replace exercise as a stress test in the evaluation of patients with left-to-right shunts and left ventricular volume load, but it imposes a lower work load on the heart because aortic blood pressure is not increased and ventricular filling pressures are slightly reduced. The lower work load was demonstrated by a lower myocardial oxygen consumption during isoproterenol infusion than during exercise. When interpreting an isoproterenol stress test, one should beware of underestimating the severity of the heart disease.

**Regional blood flow distribution.** The increase in systemic blood flow during isoproterenol infusion was directed mainly at the carcass, presumably the muscles (Chapter nine). This can be explained by the following mechanism: the adrenergic effect not only increases cardiac contractility but also dilates the vessels in the muscles (β2), thus reducing cardiac afterload. Furthermore, gastrointestinal blood flow increased which is interesting in view of the possibly decreased gastrointestinal blood flow in the shunt lambs. Finally, the heart claims part of the increased systemic blood flow to meet its increased metabolic demands.

Even during provocation with the synthetic catecholamine isoproterenol did myocardial fatty acid uptake not increase relative to other substrates, despite a threefold increase in plasma free fatty acid concentration (Chapter ten). Plasma concentration is regarded as one of the most important determinants of myocardial substrate utilization, but the results of the isoproterenol experiments demonstrate that myocardial fatty acid metabolism is more complex.

**Extracellular volume** was increased in the shunt lambs but it was all retained within the intravascular compartment through the colloid osmotic action of an increased intravascular protein mass (Chapter eleven). Left ventricular stroke volume proved to correlate with plasma volume, which illustrates its beneficial effect because a larger stroke volume helps the left ventricle to compensate for the runoff through the shunt. Future studies should substantiate if support of this physiological adaptation, for instance by early administration of intravascular protein, could be of therapeutic help. The increase in plasma volume was realized by transient increases in plasma renin activity and plasma aldosterone concentration.

Chapter twelve discusses the validity of the experimental left-to-right shunt as a model for the study of infants with left-to-right shunts and left ventricular volume load. Comparison with human data is made. The relevance of the results of the various chapters for infants is outlined and conclusions are drawn: as a result of adaptation to the left ventricular volume load by means of myocardial hypertrophy and plasma volume increase, lambs with a substantial left-to-right shunt are able to cope with a considerable additional cardiac work load. Furthermore, no deleterious effects, such as an increase in shunt flow or a compromise in myocardial blood supply occur; therefore, no arguments were found to dissuade from the policy of waiting for spontaneous reduction of a shunt.